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The energy demand of fast neuronal network oscillations: insights from brain slice preparations

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Fast neuronal network oscillations in the gamma range (30–100 Hz) in the cerebral cortex have been implicated in higher cognitive functions such as sensual perception, working memory, and, perhaps, consciousness. However, little is known about the energy demand of gamma oscillations. This is mainly caused by technical limitations that are associated with simultaneous recordings of neuronal activity and energy metabolism in small neuronal networks and at the level of mitochondria *in vivo*. Thus recent studies have focused on brain slice preparations to address the energy demand of gamma oscillations *in vitro*. Here, reports will be summarized and discussed that combined electrophysiological recordings, oxygen sensor microelectrodes, and live-cell fluorescence imaging in acutely prepared slices and organotypic slice cultures of the hippocampus from both, mouse and rat. These reports consistently show that gamma oscillations can be reliably induced in hippocampal slice preparations by different pharmacological tools. They suggest that gamma oscillations are associated with high energy demand, requiring both rapid adaptation of oxidative energy metabolism and sufficient supply with oxygen and nutrients. These findings might help to explain the exceptional vulnerability of higher cognitive functions during pathological processes of the brain, such as circulatory disturbances, genetic mitochondrial diseases, and neurodegeneration.

Keywords: cognition, gamma-band synchronization, inhibitory postsynaptic potential, membrane ion current, mitochondrial respiratory chain, neuroenergetics, pyramidal cell, tissue oxygen tension

FAST NEURONAL NETWORK OSCILLATIONS AND HIGHER COGNITIVE FUNCTIONS

Fast neuronal network oscillations in the gamma frequency band (30–100 Hz) that occur in the electroencephalogram or in local field potential recordings have been observed in virtually any mammalian cortical structure, including the neocortex and the hippocampus (Gray and Singer, 1989; Traub et al., 1996; Buzsáki and Draguhn, 2004; Bartos et al., 2007; Uhlhaas and Singer, 2010). Gamma oscillations reflect synchronous membrane potential oscillations of a large number of neurons in a given neuronal network, and they have been suggested to underlie higher cognitive functions such as sensual perception, attention, and memory formation (Lisman, 1999; Axmacher et al., 2006; Mann and Paulsen, 2007; Uhlhaas and Singer, 2010). Gamma oscillations are generated in local neuronal networks by the complex interplay of excitatory neurons and specific inhibitory interneurons, both of which communicating via chemical and, perhaps, electrical synapses (Tamás et al., 2000; Whittington and Traub, 2003; Bartos et al., 2007). Functionally, gamma oscillations bind neurons into a common temporal matrix, enabling precise temporal coding, spike timing-dependent plasticity, and formation of neuronal assemblies (Paulsen and Moser, 1998; Engel and Singer, 2001; Buzsáki and Draguhn, 2004; Axmacher et al., 2006). A characteristic feature is the long-range synchronization of gamma oscillations in remote cortical areas (König et al., 1995; Bazhenov et al., 2008). This phenomenon has been suggested to underlie binding of distributed neuronal representations and, therefore, forms a crucial neuronal prerequisite for the unity of sensual perception, attention, and, perhaps, consciousness (Engel and Singer, 2001; Fries et al., 2007; Uhlhaas and Singer, 2010). Importantly, gamma oscillations can be reliably induced in brain slice preparations *in vitro* (see below).

NEURONAL INFORMATION PROCESSING AND ENERGY DEMAND

The human brain consumes about 20% of the oxygen inspired at rest while accounting for only 2% of the body weight (Erecinska and Silver, 2001). This suggests that neuronal information processing is associated with an extraordinary high metabolic rate. In more global estimations, most of the energy consumption has been attributed to action potential generation ("spiking") and excitatory synaptic transmission (Attwell and Laughlin, 2001). However, information about the energy demands of different functional brain states, i.e., the energy demands of different forms of neuronal network activity, is widely lacking (Kann and Kovács, 2007; Cunningham and Chinnery, 2011). From the clinical medicine point of view, higher cognitive functions appear to be exceptionally vulnerable during various neurological and psychiatric brain pathologies (Hansen, 1985; McFarland et al., 2010; Uhlhaas and Singer, 2010).

Abbreviations: EPSP, excitatory postsynaptic potential; FAD, flavin adenine dinucleotide; GABA, γ-aminobutyric acid; IPSP, inhibitory postsynaptic potential; NAD(P)H, nicotinamide adenine dinucleotide (phosphate); pO_2, partial oxygen pressure.

Therefore, impairment of energy metabolism by either alterations in oxygen and nutrients supply and/or dysfunction of neuronal mitochondria might be a key pathogenic factor (Kann and Kovács, 2007; DiMauro and Schon, 2008; Distelmaier et al., 2009; Nicholls, 2009; Wallace, 2010). Strikingly, neuroenergetical aspects such as energy consumption and adaptations of energy metabolism that are associated with different forms of neuronal network activity have been less defined: gamma oscillations as a cellular correlate of higher cognitive functions are a prime example (Axmacher et al., 2006; Uhlhaas and Singer, 2010; Cunningham and Chinnery, 2011). This lack of information is mainly caused by technical limitations, (i) in the accessibility to certain cortical areas, and (ii) in the high spatiotemporal resolution that is required for simultaneous local recordings of neuronal activity and energy metabolism at the level of mitochondria *in vivo* (Kann and Kovács, 2007; Cunningham and Chinnery, 2011). In the recent years, research has thus focused on brain slice preparations, in particular from the hippocampus, to address the energy demand of gamma oscillations and the associated adaptations in energy metabolism *in vitro*. Here, I will firstly describe the features of hippocampal slice preparations as a reliable model to study both, gamma oscillations and neuroenergetics, and secondly review recent reports from various groups in the field. These reports suggest that gamma oscillations are associated with high energy demand that is counterbalanced by rapid adaptations in oxidative energy metabolism.

ACUTELY PREPARED SLICES AND ORGANOTYPIC SLICE CULTURES

Living slice preparations have been successfully made from the neocortex and the hippocampus of both, rodents and humans (McIlwain, 1951; Schwartzkroin and Andersen, 1975; Fisahn et al., 1998; Kann et al., 2005; Vreugdenhil and Toescu, 2005; Ivanov et al., 2011). Hippocampal tissue is usually cut in slices with a thickness of 300–400 μm. To minimize ischemic neuronal damage because of arrest in blood circulation, the preparation of slices is carried out quickly and in cold preparation solution that contains ion concentrations similar to the cerebrospinal fluid *in vivo* (Bischofberger et al., 2006; Kann and Kovács, 2007; Hájos and Mody, 2009). Recently, the add-on of further important substrates and nutrients has been proposed (Hájos and Mody, 2009; Zilberter et al., 2010). Notably, for investigations of hippocampal slices much higher glucose concentrations (10–26 mM) have been used compared with the brain *in vivo* (0.35–2.6 mM) because it is difficult to obtain healthy slices using lower concentrations (Kann and Kovács, 2007). Oxygenation and pH adjustment of preparation solution is achieved by a gas mixture of 95% O_2 and 5% CO_2. The high oxygen fraction is routinely used to ensure sufficient oxygen supply of healthy neurons in deeper slice layers, which ultimately depends on a steep diffusion gradient. Monitoring the interstitial partial oxygen pressure (pO_2) with oxygen sensor microelectrodes in hippocampal slices during spontaneous neuronal activity revealed that oxygen was still available in excess ($pO_2 > 150$ mmHg) at the depth of 160 μm below the slice cut surface (Kann et al., 2011). However, the pO_2 at the slice cut surface is often lower than theoretically expected and might significantly vary in experimental studies because of individual experimental settings such as size and construction of the recording chamber, temperature, as well as exchange rate of gas mixture or recording solution. Notably, the pO_2 is not monitored routinely in many studies because oxygen is provided in excess, at least in the neuronal cell layers of the upper third of the slice where electrophysiological and live-cell fluorescence imaging recordings are conducted (Kann and Kovács, 2007).

After preparation, hippocampal slices are either used for experiments in the next 10–12 h ("acutely prepared slices"; McIlwain, 1951; Schwartzkroin and Andersen, 1975) or maintained under sterile conditions on a biopore membrane in an incubator for up to weeks ("organotypic slice cultures"; Stoppini et al., 1991). It is important to note that individual neurons and neuronal networks in such slice cultures show similar morphological and functional features as compared to the hippocampus *in vivo* (Caeser and Aertsen, 1991; Bahr et al., 1995; De Simoni et al., 2003; Kann et al., 2011), including preservation of the natural cellular environment, i.e., the presence of astrocytes and microglial cells ("organotypic"). However, hippocampal slice cultures widely lack input from other (sub)cortical brain areas. After 10–14 days *in vitro* slice cultures have shorter diffusion distances for oxygen and nutrients compared to acutely prepared slices because of the residual thickness of about 200 μm. Moreover, the initially damaged slice cut surface is reorganized (Bahr et al., 1995; Kann and Kovács, 2007). During electrophysiological and/or live-cell fluorescence imaging recordings slice preparations are stored either entirely in recording solution that is saturated with the gas mixture containing 95% O_2 ("submerged condition") or at the interface between recording solution and the gas mixture ("interface condition"; Kann and Kovács, 2007; Hájos and Mody, 2009). Under the interface condition, slice preparations are still covered with a thin layer of recording solution. Usage of brain slice preparations has significantly contributed to a deeper understanding of neuronal functions at the cellular and network level in the recent decades. However, given factors such as absence of blood circulation, longer diffusion distances, steep interstitial pO_2 gradients, and composition of the recording solution have to be kept in mind when interpreting data from slice preparations (Kann and Kovács, 2007; Zilberter et al., 2010).

HIPPOCAMPAL SLICE PREPARATIONS AS A RELIABLE MODEL FOR GAMMA OSCILLATIONS

In neuronal networks of the hippocampus, pyramidal cells, and granule cells are excitatory projection neurons with long-range glutamatergic connections (releasing neurotransmitter, glutamate). Besides these projection neurons there is a population of various inhibitory GABAergic interneurons [releasing neurotransmitter, γ-aminobutyric acid (GABA)], comprising about 10% of all hippocampal neurons (Caeser and Aertsen, 1991; Freund and Buzáki, 1996; Freund, 2003). Evidence from electrophysiological recordings, high-resolution functional imaging, transgenic animals, and mathematical modeling has revealed a major role of these inhibitory interneurons in the generation of coherent activity patterns. Specific types of interneurons support broad simultaneous rhythmic inhibition and thus synchronize the activity of large neuronal populations *in vitro* and *in vivo* (Freund, 2003; Whittington and Traub, 2003; Bartos et al., 2007; Sohal et al., 2009; Gulyás et al., 2010; Korotkova et al., 2010). For gamma

oscillations, perisomatic GABAergic interneurons are of central importance because the highly divergent axonal plexus allows synchronous inhibition of 1000–2000 pyramidal cells (Freund and Buzáki, 1996; Freund, 2003; Mann and Paulsen, 2007). About 50% of these interneurons are parvalbumin-containing baskets cells that are able to generate fast series of action potentials and, thus, follow almost every gamma cycle (30–100 Hz). Pyramidal cells, by contrast, show strong spiking accommodation and have typical spiking rates around 2–4 Hz during gamma oscillations *in vitro* and *in vivo* (Csicsvari et al., 1999; Freund, 2003; Hájos et al., 2004; Gulyás et al., 2010). It is important to note that the rhythmic hippocampal oscillations that occur in local field potential recordings *in vitro* primarily reflect averaged synchronized inhibitory postsynaptic potentials (IPSPs) in the perisomatic region rather than action potentials and excitatory postsynaptic potentials (EPSPs; Mann et al., 2005; Oren et al., 2010). Similar findings were reported from slices of the occipital cortex (Trevelyan, 2009).

Sustained gamma oscillations can be reliably induced in both, acutely prepared slices and slice cultures. In most of the studies, low concentrations of acetylcholine (carbachol) or kainic acid were added to the recording solution to activate muscarinic and ionotropic glutamate receptors, respectively (Fisahn et al., 1998; Fellous and Sejnowski, 2000; Vreugdenhil and Toescu, 2005; Wójtowicz et al., 2009; Kann et al., 2011). In particular, application of acetylcholine mimics cholinergic input from the septum *in vivo*. Despite some differences in the underlying synaptic mechanisms (Bartos et al., 2007) both models share important features with hippocampal gamma oscillations *in vivo* and are commonly used for analysis and mathematical modeling of cellular and network dynamics (Whittington and Traub, 2003; Bartos et al., 2007; Hájos and Paulsen, 2009). In hippocampal slice preparations, pharmacologically induced sustained gamma oscillations occur most prominently in subfield CA3 and weaker in subfield CA1, and they are absent in the dentate gyrus. This has been observed in both acutely prepared slices and slice cultures from mouse and rat (Fisahn et al., 1998; Wójtowicz et al., 2009; Kann et al., 2011). The oscillations are widely similar to gamma oscillations *in vivo*, including the sites of intrahippocampal generation and propagation. One exception is that under certain conditions input from the entorhinal cortex might also drive gamma oscillations of lower power in the dentate gyrus *in vivo* (Csicsvari et al., 2003). Gamma oscillations *in vivo* occur in the presence and the absence of theta oscillations (6–9 Hz), in brief periods as well as prolonged periods (>10 s) during running of the animal or rapid-eye-movement (REM) sleep (Penttonen et al., 1998; Buhl et al., 2003; Buzsáki et al., 2003; Chen et al., 2011).

HIGH ENERGY DEMAND OF HIPPOCAMPAL GAMMA OSCILLATIONS

Gamma oscillations *in vitro* have been reliably induced in the interface recording condition (Traub et al., 1996; Fisahn et al., 1998). Notably, under the submerged recording condition gamma oscillations could be only induced when the exchange of recording solution was significantly improved, for example by increasing the flow rate to 5–6 ml/min and by decreasing the volume of the recording chamber (Hájos et al., 2004; Huchzermeyer et al., 2008). Further studies demonstrated rapid decreases in the power of gamma oscillations in hippocampal slice preparations, (i) when the pO_2 of the ambient atmosphere was lowered to the normoxic range under the interface recording condition (Huchzermeyer et al., 2008), (ii) when the flow rate of oxygenated recording solution was too low under the submerged recording condition (Hájos et al., 2009), and (iii) when hypoxic events were induced (Fano et al., 2007; Pietersen et al., 2009). Rapid decreases in the power of gamma oscillations were also observed during pharmacological interference with mitochondrial function, namely inhibition of the respiratory chain by rotenone (acting on complex I) or potassium cyanide (acting on cytochrome *c* oxidase in complex IV), and mitochondrial uncoupling by protonophores (Kann et al., 2011; Whittaker et al., 2011). Moreover, the exquisite sensitivity of gamma oscillations to mitochondrial dysfunction has been identified because other activity forms such as electrical stimulus-evoked neuronal activation and pathological seizure-like events were more resistant to both, respiratory chain inhibition and low pO_2 (Huchzermeyer et al., 2008; Kann et al., 2011). Similar observations were recently made during unilateral hippocampal ischemia *in vivo* (Barth and Mody, 2011). These studies consistently show that hippocampal gamma oscillations are rapidly impaired during metabolic stress, indirectly suggestive for a high energy demand. Mechanistically, fast-spiking inhibitory interneurons might play a crucial role in this rapid impairment because of their key role for establishment of gamma oscillations as well as the unique electrophysiological and biochemical properties when compared to excitatory projection neurons (Gulyás et al., 2006; Alle et al., 2009; Carter and Bean, 2009; Hasenstaub et al., 2010; Kann et al., 2011; Whittaker et al., 2011).

More direct evidence for the high energy demand of gamma oscillations was recently provided by combining local field potential and pO_2 recordings. It was demonstrated that the power of gamma oscillations positively correlated with a substantial increase in oxygen consumption in both, acutely prepared slices and slice cultures. Intriguingly, the level of oxygen consumption as determined during gamma oscillations reached the level that was observed during a strong pathological form of neuronal activity, namely seizure-like events (Kann et al., 2011). These data clearly substantiate the notion that hippocampal gamma oscillations *in vitro* are associated with high oxygen consumption. This is in line with an *in vivo* study from the cat visual cortex describing tight correlations between gamma oscillations and hemodynamic responses (Niessing et al., 2005) that might reflect local adaptations in blood flow to increase oxygen and nutrients supply (Leybaert, 2005; Attwell et al., 2010; Cauli and Hamel, 2010).

The high oxygen consumption during gamma oscillations might be explained by several mechanisms underlying neuronal signaling. Both, excitatory pyramidal cells and inhibitory GABAergic interneurons increase their spiking rates from different base levels during gamma oscillations. This would increase the energy demand in these neurons, despite the fact that diverse neuronal subtypes might feature different biophysical properties for energy cost efficient generation of action potentials (Hasenstaub et al., 2010). As a consequence of increased spiking rates and highly divergent connectivity, and this might be more relevant for the increased energy demand during gamma oscillations, the incidence of EPSPs and IPSPs in the neuronal network massively

increases, and thus ion fluxes through neuronal membranes as well (De Simoni et al., 2003; Whittington and Traub, 2003; Mann and Paulsen, 2007). The ion fluxes tend to dissipate the concentration gradients of Na^+, Ca^{2+}, K^+, and Cl^- ions that exist across neuronal membranes to ensure proper neuronal function. In order to maintain ionic homeostasis, the concentration gradients are continuously reconstituted against electrochemical equilibrium by ion pumps such as Na^+/K^+-ATPase and Ca^{2+}-ATPase as well as transporters such as Na^+/Ca^{2+}-exchanger and $Na^+/K^+/Cl^-$-cotransporter. These transport processes are finally energy-dependent, leading to breakdown of cellular energy carrier, ATP (Attwell and Iadecola, 2002; Kann and Kovács, 2007). In the brain, most of the ATP generation has been attributed to oxidative phosphorylation in mitochondria (Erecinska and Silver, 2001; Attwell and Iadecola, 2002) and neurometabolic coupling is rapidly mediated by changes in substrate ratios as well as cytosolic and mitochondrial Ca^{2+}-signaling (Duchen, 1992; Kann et al., 2003; Leybaert, 2005; Kann and Kovács, 2007). Therefore, the high oxygen consumption as observed during gamma oscillations might reflect fast adaptations in mitochondrial oxidative energy metabolism. However, further experimental studies are required to determine the potential contribution of energy substrates other than glucose as well as the roles of aerobic and anaerobic glycolysis (Magistretti and Pellerin, 1999; Raichle and Mintun, 2006; Schurr, 2006; Schousboe et al., 2007; Gallagher et al., 2009; Ivanov et al., 2011).

In several reports, live-cell fluorescence imaging of nicotinamide adenine dinucleotide (phosphate) and flavin adenine dinucleotide [NAD(P)H, FAD] was applied to get insight into neuronal activity-dependent changes in mitochondrial redox state, and thus adaptations in energy metabolism (Duchen, 1992; Kann et al., 2003; Kasischke et al., 2004; Brennan et al., 2006; Ivanov et al., 2011). Using this imaging technique the changes in mitochondrial redox state during gamma oscillations were recently investigated in slice cultures. Interestingly, gamma oscillations were associated with a shift toward reduction of the dinucleotides although the interstitial pO_2 was hyperoxic (Huchzermeyer et al., 2008). This observation might reflect an increase in the availability of substrates as a result of enhanced glycolysis in neuronal and astrocytic compartments (Kasischke et al., 2004; Brennan et al., 2006; Hertz et al., 2007) or an imbalance of neuronal tricarboxylic acid cycle and mitochondrial respiratory chain activities. Moreover, repetitive electrical stimulation that was additionally applied during gamma oscillations resulted in significantly smaller shifts toward oxidation of the dinucleotides compared to controls (Kann et al., 2011). These data suggest that hippocampal gamma oscillations are associated with near-limit utilization of mitochondrial oxidative capacity, and thus provide further evidence for the high energy demand during gamma oscillations. The data might also imply that rapid and sufficient supply of oxygen and nutrients is a fundamental prerequisite for the maintenance of fast neuronal network oscillations.

Intriguingly, the electrophysiological and biochemical features of hippocampal subfield CA3, namely highest levels in gamma oscillation power, oxygen consumption, and mitochondrial performance, also correlated with the highest expression of mitochondrial complex I subunits (Kann et al., 2011; Wirtz and Schuelke, 2011). Complex I (NADH:ubiquinone oxidoreductase) is part of the mitochondrial respiratory chain and composed of up to 46 individual subunits. These subunits are encoded by both, nuclear and mitochondrial DNA (Distelmaier et al., 2009). Mitochondrial complex I has been discussed to exert major control over oxidative phosphorylation, and to play a key role in the pathogenesis of neurodegenerative diseases (Pathak and Davey, 2008). The pattern of complex I gene expression in the hippocampus might reflect unique enzymatic properties of neuronal mitochondria in subfield CA3 to match the high energy demand that is associated with the generation of gamma oscillations (Kann et al., 2011).

IMPLICATIONS FOR CLINICAL MEDICINE

It has been known from animals and humans that higher sensory and motor functions are much more vulnerable to metabolic stress than basic responses of neurons to extrinsic electrical stimuli and ion distributions in neuronal tissue (Rossen et al., 1943; Hossmann and Sato, 1970; Hansen, 1985). However, the underlying cellular mechanisms are still unknown. Gamma oscillations have been discussed as a cellular correlate of higher cognitive functions (Lisman, 1999; Axmacher et al., 2006; Mann and Paulsen, 2007; Uhlhaas and Singer, 2010). Thus, the recent neuroenergetical data on gamma oscillations in brain slice preparations and the proposed mechanisms as outlined above might contribute to a more comprehensive understanding of the exceptional vulnerability of higher brain functions during circulatory disturbances, mitochondrial diseases, and neurodegeneration.

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