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NMDA Receptors Pattern Early Activity in the Developing Barrel Cortex In Vivo

Marat Minlebaev, Yehezkiel Ben-Ari and Roustem Khazipov

The Mediterranean Institute of Neurobiology, Institut National de la Sante et de la Recherche Medicale U901, Universite' Mediterreneen, Marseille, France

N-methyl-D-aspartate (NMDA) type of glutamate receptors play an important role in activity-dependent plasticity in the developing cortex. However, the physiological patterns of cortical activity that activate NMDA receptors in vivo remain largely unknown. We performed full-band recordings from the barrel cortex of neonatal rats in vivo and found that the dominant pattern of the early activity, network driven spindle bursts, are associated with large amplitude NMDA receptor–dependent delta waves. The major sink of delta waves was in the dense cortical plate, which coincided with the sinks of sensory-evoked responses as well as fast spindle-burst oscillations. Pharmacological analysis revealed major contributions from NMDA and alpha-aminopropionate (AMPA) type of glutamate receptors in the generation of delta waves, whereas fast oscillations primarily involved only AMPA receptors. Our results suggest that the 2 component spindle burst is generated by rhythmic, presumably thalamocortical, synaptic input which entrains an AMPA receptor-mediated fast oscillation and who's summation generates an NMDA and AMPA receptor mediated delta wave. The massive summation of thalamocortical activity during the spindle bursts thus provides a long time window for co-incident activation of cortical neurons by the thalamocortical cells which may contribute to the formation of thalamocortical synapses in the barrel cortex during the critical period of developmental plasticity.

Keywords: delta-brush, delta waves, electroencephalography, neonate, NMDA, rat

Introduction

During development, coordinated neuronal activity plays an important role in cortical development, particularly during so-called critical periods of developmental plasticity (Rakic and Komuro 1995; Katz and Shatz 1996; Komuro and Rakic 1998; Feldman et al. 1999; Zhang and Poo 2001; Crowley and Katz 2002; Fox 2002; Katz and Crowley 2002; Foeller and Feldman 2004; Feller and Scanziani 2005; Moody and Bosma 2005; Price et al. 2006). In the neonatal rat barrel cortex, thalamocortical synapses demonstrate one such critical period during the first postnatal week. During this period, thalamocortical axons grow into neocortex and form whisker-specific barrel pattern of synapses with neocortical neurons (Woolsey and Van der Loos 1970; Erzurumlu and Jhaveri 1990; Higashi et al. 2002; Molnar et al. 2003a; Price et al. 2006; Petersen 2007). Manipulations of the peripheral receptors, or of cortical activity, during this critical period can disrupt the formation of thalamocortical synapses (Van der Loos and Woolsey 1973; Woolsey and Wann 1976; Fox 1992; O'Leary et al. 1994; Cases et al. 1996; Catalano and Shatz 1998; Feldman et al. 1999; Persico et al. 2001; Fox 2002; Foeller and Feldman 2004; Fox and Wong 2005; Lu et al. 2006). Pharmacological or genetic manipulations associated with a loss of function of NMDA type of glutamate receptors (NMDA-Rs) result in malformations of barrel cortex development and functional deficits (Schlaggar et al. 1993; Fox et al. 1996; Iwasato et al. 2000; Fox 2002; Dagnew et al. 2003; Lee et al. 2005a, 2005b). During the critical period, thalamocortical synapses display an enhanced NMDA-R contribution, and increased NMDA-R–dependent synaptic plasticity including the conversion of "silent" pure NMDA-R based synapses to fully functional mixed alpha-aminopropionate (AMPA)/NMDA-R synapses, as well as a switch to fast AMPA receptor mediated synaptic transmission from slow kainate mediated transmission (LoTurco et al. 1991; Carmignoto and Vicini 1992; Hestrin 1992; Monyer et al. 1994; Crair and Malenka 1995; Isaac et al. 1995b; Isaac et al. 1997; Feldman et al. 1998; Feldman et al. 1999; Barth and Malenka 2001; Bannister et al. 2005; Daw et al. 2006). Despite the important developmental role for NMDA-Rs in the formation of thalamocortical synapses, little is known on the physiological in vivo network activity patterns associated with activation of NMDA-Rs.

Almost all neuronal activity in barrel cortex during the critical developmental period occurs as part of a 200- to 600-ms oscillatory burst known as a "spindle burst," which is composed of a rapid oscillation in the alpha–beta (8–25 Hz) frequency range nested in an envelope of delta wave (1–4 Hz) (Khazipov et al. 2004; Minlebaev et al. 2007). Spindle bursts are homologous to an electrographic pattern of delta-brushes in the human premature neonates (Anderson et al. 1985; Stockard-Pope et al. 1992; Lamblin et al. 1999; Vanhatalo et al. 2002; Vanhatalo et al. 2005; Khazipov and Luhmann 2006; Scher 2006; Milh et al. 2007). The spindle burst is an endogenous pattern of activity, which is reliably triggered by peripheral stimulation but persists after deafferentation (Khazipov et al. 2004; Hanganu et al. 2006). In the intact animals, somatosensory spindle bursts are driven by satisfy feedback resulting from spontaneous myoclonic twitches (Khazipov et al. 2004; Milh et al. 2007), a characteristic pattern of motor activity during early development (de Vries et al. 1982; Cioni and Prechtl 1990; Blumberg and Lucas 1994; O'Donovan 1999; Petersson et al. 2003). Our previous studies of spindle bursts have focused on the rapid oscillatory component and showed them to be mediated by glutamatergic synapses, primarily through AMPA receptors (Khazipov et al. 2004; Hanganu et al. 2006; Minlebaev et al. 2007). However, in these previous studies only frequencies above 1–3 Hz were evaluated, which likely compromised the slow delta component of spindle bursts as well as contributions of slow NMDA-R mediated currents. Therefore, the nature of delta waves and NMDA-Rs contributions to spindle bursts remain largely under explored.

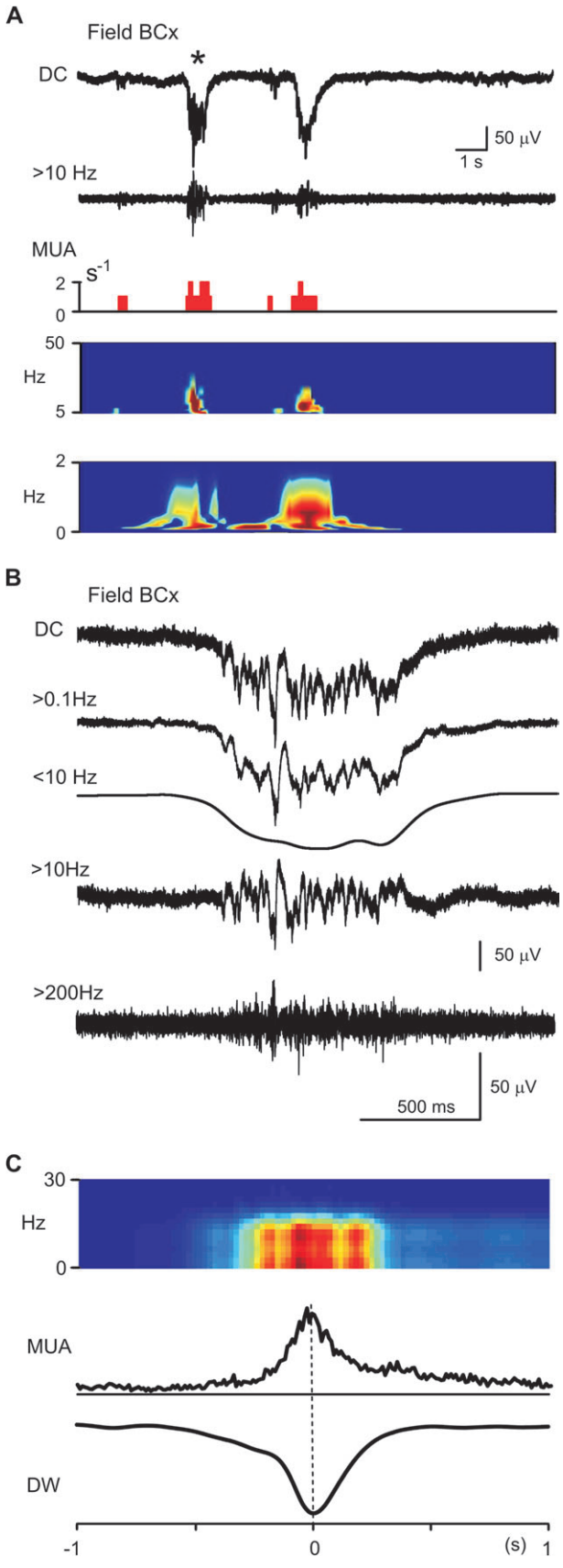

Figure 1. Spindle bursts in the neonatal rat barrel cortex consist of delta waves nesting alpha–beta oscillations. (*A*) Field potential recordings from the P4 rat superfused barrel cortex (BCx) in DC and >10 Hz high-pass AC modes (top traces); below are shown the corresponding MUA and time-frequency analysis in 5–50 Hz and 0.1–2 Hz ranges. (*B*) The spindle burst marked by black asterisk on panel A is shown on an expanded time scale in different modes of frequency filters. (*C*) Cross correlation of the power in alpha–beta frequency characteristic of spindle-burst oscillations (top) and cortical units activity (middle) versus delta wave (average of 51 delta waves).

In the present study, we have explored the network mechanisms of the delta component of spindle bursts using full-band depth electroencephalography and multiunit recordings in the neonatal rat barrel cortex. We show that delta component of spindle bursts is generated by summation of synaptic currents in glutamatergic, presumably thalamocortical synapses, with an important contribution of the currents through NMDA-Rs that efficiently summate because of their slow kinetics. The massive summation of thalamocortical activity during the spindle bursts thus provides a long time window for co-incident activation of cortical neurons by the thalamocortical cells that may contribute to the NMDA-R–dependent formation of thalamocortical synapses in the barrel cortex during the critical period of developmental plasticity.

Materials and Methods

This study followed INSERM guidelines on animal care, with approval from the animal care and use local committee. Wistar rats of both sexes from postnatal days [P] 1–6 were used. P0 was the day of birth. During the surgical procedure, rats were anesthetized with a combination of 0.5–1.5 g/kg urethane injected intraperitoneally and ice-cooling. Surgical procedures and installation of the perfusion chamber were performed as described previously (Khazipov and Holmes 2003; Minlebaev et al. 2007). During recordings, rats were heated via a thermal pad (37 °C). The chamber was perfused with oxygenated (95% O_2 and 5% CO_2) artificial cerebrospinal fluid (ACSF) of the following composition (in mM): 126 NaCl, 3.5 KCl, 2.0 $CaCl_2$, 1.3 $MgCl_2$, 25 $NaHCO_3$, 1.2 NaH_2PO_4, and 11 glucose, pH 7.4 at a rate of 2 mL/min. Temperature in the chamber was kept at 35–37 °C using an automatic temperature controller (TC-344B; Warner Instruments, Hamden, CT). Extracellular field potential recordings were performed: 1) in direct-current (DC) coupled mode, using ASCF-filled glass electrodes (resistance 1–3 MOhms) connected to the amplifier input via chlorided argentum wire; or 2) in alternating current (AC) coupled mode (high-pass filter >0.1 Hz), using tungsten electrodes of 50 μm in diameter (California Fine Wire, Grover Beach, CA) and 16 channel silicon probes with 100 μm separation distance between the channels (Neuronexus Technologies, MI). AC mode with low values of high-pass filters was used for tungsten electrodes and silicone probes because of the large offset exceeding the input diapason and saturating the amplifier in DC mode. Comparison of delta waves recorded simultaneously using glass electrodes in DC mode and tungsten electrodes with >0.1 Hz high-pass did not reveal any significant difference in their amplitude, duration and waveform (Fig. 1*B*). Afferent stimulation was performed as indicated: 1) by global whisker pad stimulation by electrical pulses (60 V, 50 μs, 0.03/s) through pairs of electrodes inserted into the whisker pads and fixed to the skin with super glue, or 2) by single whisker stimulation using electromechanic device (200 ms, amplitude 2 mm, 0.03/s). Signals were amplified (x1000) using 2 4-channel amplifiers DAM8A (total 8 channels) (World Precision Instruments, UK) and recorded in DC or low-values AC (high-pass filtering >0.1 Hz) modes.

Whole-cell recordings of the pharmacologically isolated spontaneous AMPA and NMDA-R mediated synaptic currents were performed from the barrel cortex dense cortical plate in the cortical slices prepared from P3 rat pups in vitro. Coronal brain slices (300 μm thick) were prepared using a Microm tissue slicer (International GmbH, Germany). Slices were kept in oxygenated (95% O_2/5% CO_2) ACSF at room temperature (20–22 °C) at least 1 h before use. For recordings, slices were placed into a conventional fully submerged chamber superfused with ACSF at a rate of 2–3 mL/min at 34–35 °C. Patch clamp recordings

from visually identified pyramidal cells of the dense cortical plate in whole-cell configuration were performed using EPC-10 amplifier (HEKA Elektronik Dr. Schulze GmbH, Lambrecht/Pfalz, Germany). The pipettes were filled with a solution of the following composition (in mM): 130 Cs-gluconate, 13 CsCl, 0.1 $CaCl_2$, 1 ethylene glycol tetraacetic acid (EGTA), and 10 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES) (pH 7.25). Membrane potential values were corrected for liquid junction potential of +8 mV.

All data were digitized at 10 kHz using Digidata 1440 interface (Axon Instruments) and analyzed offline using an Axon package (Axon Instruments), MiniAnalysis (Synaptosoft, Decatur, GA), Origin (Microcal Software, Northampton, MA) and Matlab (MathWorks, Natick, MA). Group measures are expressed as means ± SE. The statistical significance of differences was assessed with the Student's *t*-test. The level of significance was set at $P < 0.05$. Drugs were purchased Tocris Neuramin (Bristol, UK) (gabazine, CNQX, D-APV), and all other compounds from Sigma (St Louis, MO).

Results

Delta Component of Spindle Bursts

In the present study, we have studied the delta component of spindle bursts in the neonatal rat (P1–6) barrel cortex using a superfused neocortex preparation in vivo (Minlebaev et al. 2007). DC- or low-value high-pass (>0.1 Hz) AC recordings were employed to resolve the delta component. In general agreement with previous studies (Khazipov et al. 2004; Minlebaev et al. 2007), electrical activity in the barrel cortex during the first postnatal week was highly discontinuous and was organized in intermittent spindle bursts occurring at a rate 2.9 ± 0.5/min (mean ± SEM; $n = 19$; P1–6, depth 400–600 μm). As evidenced by wavelet time–frequency analysis, spindle bursts are associated with alpha–beta oscillations and bursts of multiple unit activity (MUA) nested in a negative delta wave (Fig. 1). The duration of delta waves was of 782 ± 17 ms ($n = 19$ rats, 454 events, P1–6) which was the same as the duration of spindle bursts (Fig. 2*B*). However, delta waves were significantly larger than in previous studies, attaining several hundreds of microvolts in amplitude (280 ± 53 μV; $n = 19$ rats, 454 events) (Fig. 2*A*). High-pass filtering at >1–3 Hz as employed in previous studies strongly reduced the amplitude of delta waves (Fig. 1*A*,*B*). Low pass filtering at <10 Hz did not change significantly the amplitude of delta component of spindle burst (280 ± 53 μV before and 237 ± 32 μV after filtering, $n = 19$ rats, 454 events, $P > 0.05$, $t = 1.68$) but efficiently suppressed the rapid oscillatory component (Fig. 1*B*). This low pass filtering was used to isolate and characterize the properties of the delta component. Thus, spindle bursts are associated with robust delta waves, which are greatly compromised by high-pass filtering in the ranges commonly employed during standard microelectrode recording.

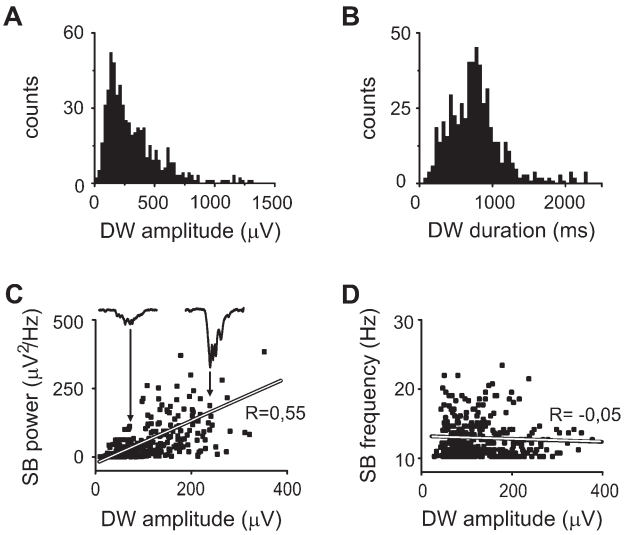

Figure 2. Quantitative relationships between the delta wave and alpha–beta oscillatory component of spindle bursts. (*A*, *B*) Distribution of amplitude (*A*) and duration (*B*) of delta waves associated with spontaneous spindle bursts ($n = 19$ rats, 454 events, P1–6). (*C*, *D*) Dependence of the power (*C*) and frequency (*D*) of rapid oscillatory component of spindle bursts on the amplitude of delta wave of spontaneous spindle bursts. Each point corresponds to individual spindle burst ($n = 390$ spindle bursts; P3–5 animals).

Relationships between the Delta Waves and Alpha–Beta Oscillations

We further studied the temporal and quantitative relationships between the 2 principal components of spindle bursts, the alpha–beta oscillation and the delta wave. Analysis of the temporal relationship was obtained by making a delta-wave triggered average of the frequency power of alpha–beta oscillations (8–21 Hz) and MUA frequency. We found that the peak of alpha–beta oscillations and MUA frequency occurs at the peak of negativity of the delta waves (Fig. 1*B*,*C*). Analysis of the quantitative relationships between alpha–beta oscillations and delta waves also revealed strong correlation between these 2 spindle burst components. Calculated for each individual spindle burst, the power of the alpha–beta oscillation was positively correlated with delta wave amplitude ($r = 0.55$; $n = 390$ spindle bursts; P3–5 animals) (Fig. 2*C*). There was no significant correlation between the peak frequency of alpha–beta oscillations and delta wave amplitude (Fig. 2*D*). Taken together, these results indicate that there is a tight correspondence of time and size between the 2 main constituents of spindle burst, alpha–beta oscillation and delta wave.

Sensory-Evoked Delta Waves

Spindle bursts can be reliably evoked by direct sensory stimulation of the topographically appropriate body part (Khazipov et al. 2004; Minlebaev et al. 2007). We therefore studied whether sensory evoked spindle bursts contain a delta wave component (Fig. 3). Global whisker pad electrical stimulation ($n = 11$) and single whisker mechanical stimulation ($n = 7$) evoked a sensory potential followed, with a probability of ≈0.8 by spindle bursts consisting of alpha–beta oscillation and delta wave. Sensory-evoked delta waves had an amplitude of 283 ± 44 μV, which was not significantly different from the amplitude of spontaneous delta waves (279 ± 29 μV, $P > 0.05$, $t = -0.09$), but were shorter in duration (517 ± 36 ms) than spontaneous events (759 ± 25 ms; $P < 0.05$, $t = 3.81$) ($n = 11$ rats, 290 spontaneous and 230 evoked events, respectively) (Fig. 4*A*,*B* top traces).

Current Source Density Analysis

We further studied the transcortical current source density (CSD) of sensory evoked delta waves and compared them with the CSDs of the alpha–beta components and the sensory evoked potentials. For this purpose, we used 8 channels of a multisite linear electrode array with 200 μm depth increments (Fig. 3*A*). CSD analysis of the delta wave revealed

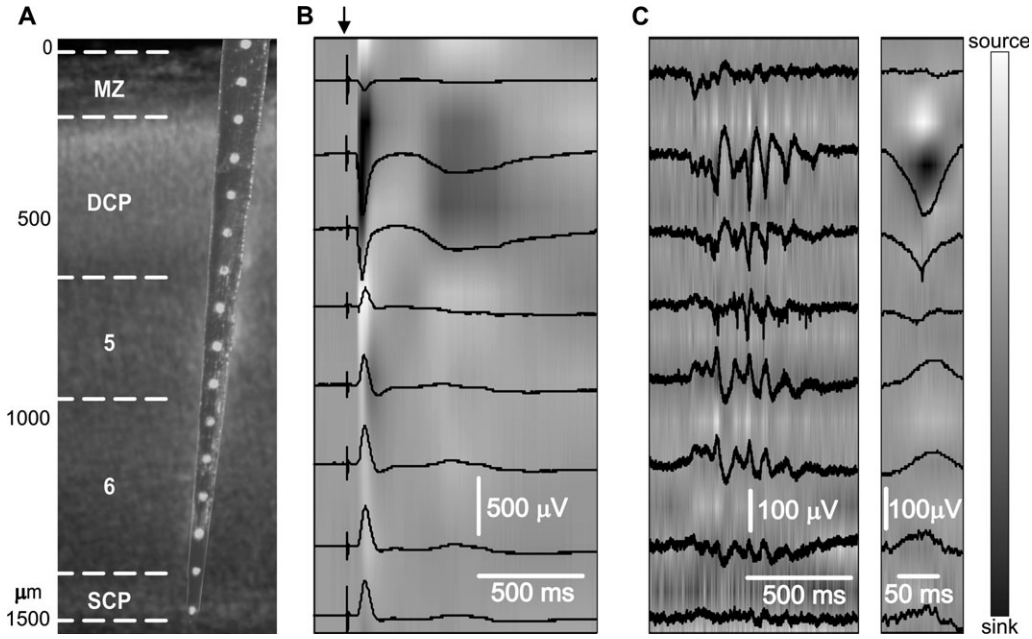

Figure 3. Transcortical depth profile of sensory-evoked potential and spindle-burst components, delta waves and alpha–beta oscillations. (*A*) Microphotograph of a coronal barrel cortex section labeled with fluorescent cresyl. MZ, marginal zone; DCP, dense cortical plate; SCP, subcortical plate; depth from the cortical surface is indicated on the left. Recording multisite silicone probe is overlaid on DiI stained trace. (*B*) Depth profile of the sensory evoked potentials and evoked spindle burst in the superfused barrel cortex (P4 rat, average of 40 events). Note that depth profile of sensory response coincides with the depth profile of evoked delta wave. Sensory responses were evoked by single whisker stimulation (amplitude of displacement 2 mm, duration 200 ms) marked by arrow. (*C*) Depth profile of the alpha–beta oscillatory component of spindle burst (recordings were high-pass filtered at >5 Hz to suppress delta component; traces are from the same experiment as shown in (*B*). Averaged troughs of alpha–beta oscillations are shown on the right panel.

a primary sink in the dense cortical plate, at the depth between 250–600 µm with the major sink at 467 ± 10 µm (n = 5 rats; Fig. 3*B*). Delta wave CSDs were similar to the CSDs of sensory-evoked potentials and alpha–beta spindle-burst component, which had sinks at depths of 250–550 µm (mean = 477 ± 30 µm; Fig. 3*B*) and 340–470 µm (mean = 390 ± 17 µm; Fig. 3*C*), respectively (P3–4, n = 5 rats). Taken together with the CSDs of the thalamocortical responses in vitro and with the anatomical data indicating the principal location of thalamocortical synapses in the dense cortical plate at this developmental stage (Molnar et al. 2003b), present results suggest that thalamic input, which conveys sensory information to the cortex, is involved in the generation of both spindle-burst components.

Pharmacological Analysis of Delta Waves

We then studied pharmacological properties of delta waves using a superfused neocortex preparation in which dura is removed over a surface of several millimeters and the exposed cortex is superfused with ACSF. This preparation enables to apply drugs directly to the superfused cortex. Application of the AMPA/kainate receptors antagonist CNQX (20 µM) decreased the amplitude of delta waves: spontaneous delta waves were reduced from 283 ± 43 to 224 ± 29 µV (by 19 ± 3%; n = 8, P3–5, P < 0.05, t = 3.19), and sensory-evoked delta waves showed a reduction from 308 ± 29 to 231 ± 31 µV (by 25 ± 7%; n = 9, P3–5, P < 0.05, t = 2.99) (Figs 4 and 5). Blockade of AMPA/kainate receptors did not significantly affect the duration of delta waves. In keeping with the results of previous study (Minlebaev et al. 2007) CNQX near completely suppressed alpha–beta oscillatory component of spindle bursts.

Superfusion with the NMDA-R antagonist D-APV, strongly reduced the amplitude and shortened the duration of delta waves, both spontaneous and sensory evoked. The amplitude of spontaneous delta waves was reduced by d-APV (80 µM) from 306 ± 40 to 122 ± 34 µV (by 59 ± 10%; n = 10, P1–6, P < 0.05, t = 4.97), and the amplitude of sensory-evoked delta waves was reduced from 274 ± 58 to 156 ± 38 µV (by 46 ± 5%; n = 8, P1–6, P < 0.05, t = 4.56). D-APV significantly shortened both spontaneous (from 862 ± 17 to 479 ± 158 ms) and sensory evoked delta waves (from 517 ± 36 to 372 ± 21 ms) by 43 ± 19% and 23 ± 6%, respectively (n = 8, P1–6, P < 0.05, t = 3.40 and t = 3.17). In keeping with results of previous study (Minlebaev et al. 2007), D-APV did not significantly affect the rapid oscillatory component of spindle bursts.

Combined application of CNQX (20 µM) and D-APV (80 µM, n = 8 rats and 20 µM, n = 4 rats) completely eliminated delta waves associated with spontaneous and sensory evoked spindle bursts. We did not find any significant age-dependence in the sensitivity of delta and alpha–beta components of spindle bursts to the blockers of glutamate receptors within the developmental period from P1 to P6 (data not shown). However, in the presence of CNQX and D-APV, bursts of MUA activity still could be evoked by sensory stimulation. These may reflect action potentials in the afferent thalamocortical fibers, but this was not explored in the present study. Thus, both local field potential components of spindle bursts, the alpha–beta oscillations and delta waves, were completely suppressed by combined application of the ionotropic glutamate receptor antagonists suggesting their common glutamatergic origin. However, AMPA/kainate and NMDA receptors differently contribute to the delta waves and alpha–beta components of spindle bursts.

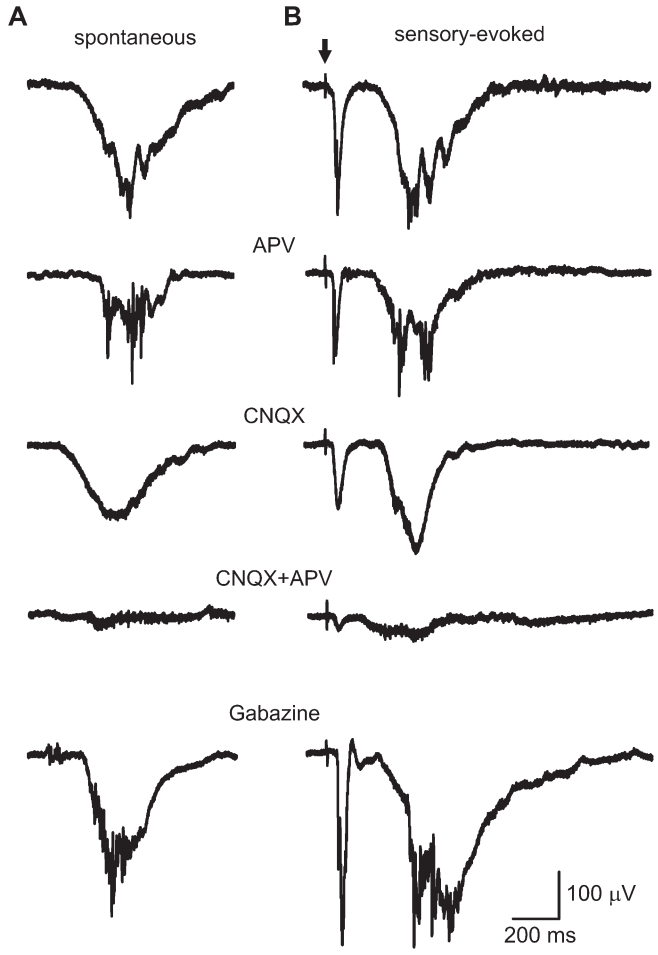

Figure 4. The effects of the antagonists of ionotropic glutamate and GABA receptors on the delta wave component of spindle bursts. (*A*) spontaneous spindle bursts, (*B*) sensory-evoked spindle bursts with sensory evoked potentials in control conditions (top traces) and in the presence of the antagonists of NMDA receptors (D-APV 80 μM), AMPA/kainate receptors (CNQX 20μM), a combination of CNQX/DAPV, GABA(A) receptors (gabazine 40 μM) (P4 rat).

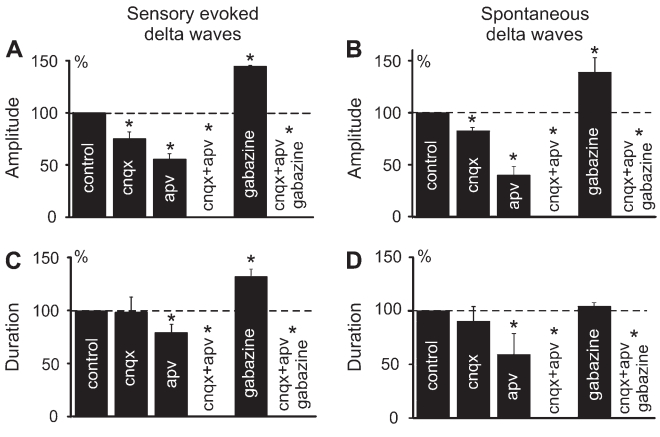

Figure 5. Pharmacological profile of the delta wave component of spindle bursts. Summary plots of the amplitudes (top panes) and durations (bottom panes) of the sensory evoked (*A, C*) and spontaneous (*B, D*) spindle bursts recorded in the presence of CNQX (20 μM; $n = 7$ P2–5 rats), D-APV (80 μM; $n = 5$ P2–5 rats), CNQX+D-APV ($n = 6$ P2–5 rats), gabazine (40 μM; $n = 5$ P2–5 rats), and CNQX/DAPV/gabazine ($n = 5$ P2–5 rats).

Because gamma-aminobutyric acidergic (GABAergic) interneurons are activated during spindle busts and participate in their spatial compartmentalization (Minlebaev et al. 2007), we have also studied the effect of the GABA(A) receptor antagonist gabazine on delta waves (Fig. 4 and 5). Application of gabazine (40 μM) significantly increased the amplitude of spontaneous and evoked delta waves to 138 ± 13% (from 291 ± 31 to 401 ± 57 μV, $n = 4$; P3–4 $P < 0.05$, $t = -2.07$) and to 144 ± 1% (from 280 ± 33 to 403 ± 55 μV, $t = -2.92$, $n = 4$; P3–4 $P < 0.05$), respectively. Blockade of the GABA(A) receptors also prolonged the duration of evoked delta waves by 132 ± 7% (from 478 ± 54 to 635 ± 35 ms) ($n = 5$; P3–4 $P < 0.05$, $t = -3.36$), but did not significantly affect the duration of spontaneous delta waves (105 ± 3%; from 759 ± 25 to 799 ± 25 ms; $n = 5$; P3–4 $P > 0.05$, $t = -0.41$). These results suggest that interneurons play an inhibitory role in spindle-bursts generation counterbalancing glutamatergic excitation during delta waves.

Gap junctions have also been suggested to play inhibitory role in spindle-bursts generation because the gap-junction antagonists increase the frequency of spindle-bursts occurrence yet without affecting the rapid oscillatory component (Minlebaev et al. 2007). In agreement with previous results, we found that application of the gap-junction blocker carbonaxolone (100 μM) increased spindle-bursts occurrence from 2 ± 0.6/min to 3.2 ± 0.8/min (by 70 ± 34%; $n = 4$, P2–5, $P > 0.05$, $t = -2.31$). This was accompanied by an increase in the amplitude of the delta component of spontaneous spindle bursts from 281 ± 69 μV to 407 ± 55 μV (by 58 ± 19%; $n = 4$, P2–5, $P < 0.05$, $t = -4.81$). These results provide additional evidence to the hypothesis that gap junctions play inhibitory role in the generation of spindle bursts in vivo, that is different from their roles in the generation of certain cortical neuronal network patterns of activity in vitro that are blocked by the gap-junctions antagonists (Yuste et al. 1992; Kandler and Katz 1995; Yuste et al. 1995; Kandler and Katz 1998a; Kandler and Katz 1998b; Peinado 2000; Peinado 2001; Dupont et al. 2006; Crepel et al. 2007).

Modeling the Glutamatergic Components of Spindle Burst

The present results are compatible with the hypothesis that spindle bursts are generated by a rhythmically active glutamatergic input, which consists of an AMPA receptor–mediated alpha–beta oscillation and whose summation generates an NMDA and AMPA receptor mediated delta wave. To test this hypothesis, we modeled integral response generated by the summation of measured AMPA and NMDA receptor mediated conductances. Pharmacologically isolated spontaneous AMPA and NMDA receptor mediated postsynaptic currents were recorded from the cortical plate neurons using barrel cortex slices in vitro in the presence of bicuculline (10 μM) and D-APV (40 μM) at holding potential of –70 mV, and in the presence of bicuculline (10 μM) and CNQX (10 μM) at holding potential of +50 mV, respectively (Fig. 6*A,B*). The amplitudes, rise-times, and the decay time constants for the AMPA receptor mediated currents were of 15 ± 1 pA, 0.7 ± 0.1 ms, 3.4 ± 0.4 ms ($n = 6$ cells) and for the NMDA receptor mediated currents were of 28 ± 2 pA, 12 ± 3 ms, 114 ± 11 ms ($n = 3$ cells). Results of a model of the summation of 10 average AMPA and NMDA mediated synaptic events occurring with 50-ms intervals (that corresponds to the mean frequency of spindle-burst rapid oscillatory component) are shown on Figure 6*B*. AMPA

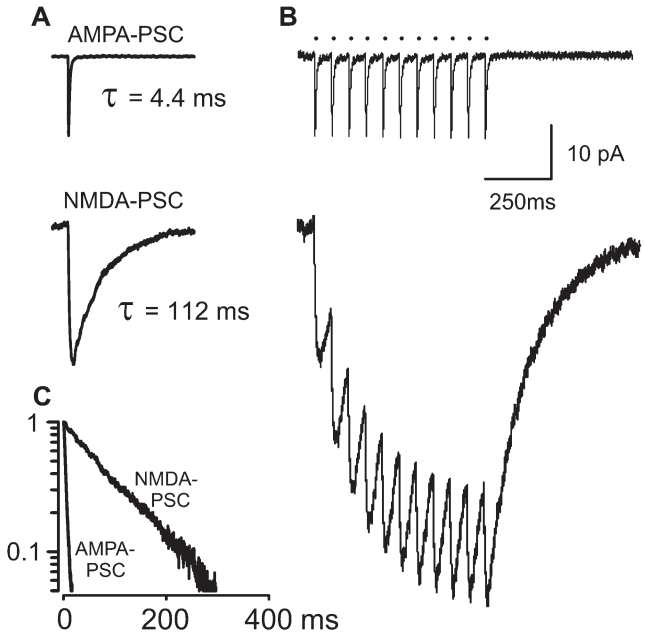

Figure 6. Modeling of spindle burst. (*A*) AMPA (upper trace) and NMDA (bottom trace) receptors mediated components of the glutamatergic postsynaptic currents (PSCs) recorded from the cortical plate neurons from a P3 rat barrel cortex slice. Traces represent an average of 183 and 193 synaptic events, respectively. AMPA-PSCs were recorded in the presence of bicuculline (10 μM) and D-APV (40 μM) at holding potential −70 mV. NMDA-PSCs were recorded in the presence of bicuculline (10 μM) and CNQX (10 μM) at holding potential +50 mV to avoid the magnesium block and are inverted for clarity. (*B*) The decays of the averaged AMPA and NMDA-PSCs are plotted in a semi logarithmic scale. (*C*) Results of a computer summation of a train of the AMPA-PSCs and NMDA-PSCs (10 events with 50-ms interevent intervals). Note that the AMPA-PSCs do not summate but with a high confidence transmit 20-Hz rhythmic input, whereas NMDA-PSCs summate and generate a delta wave-like event.

receptor mediated component alone showed little summation because of short duration of the individual AMPA-R mediated postsynaptic currents. However, NMDA-R mediated synaptic events displayed strong summation giving rise to a delta wave-like event. These results are in agreement with the hypothesis that the 2 component spindle burst is generated by summation of the glutamatergic synaptic input with fast AMPA receptor mediated component entraining alpha–beta oscillation and summated NMDA-Rs mediated component generating delta wave.

Discussion

The principal findings of the present study are as follows: 1) the previously identified primary pattern of cortical activity in the neonatal cortex, the "spindle burst" is actually a 2 component pattern consisting of a rapid alpha–beta oscillation (the spindle) and a slow depolarization of delta frequency ("delta wave"); 2) these 2 components have strong temporal and quantitative correlations, CSD profiles coinciding with the sensory evoked responses, and share a glutamatergic nature and therefore likely result from the same inputs; 3) the generation of delta waves involves primarily an NMDA and AMPA receptor mediated currents and GABAergic interneurons and gap-junctions inhibit delta waves. Together these results suggest that alpha–beta and delta components of spindle bursts share common glutamatergic—presumably thalamocortical—synaptic drive, but are primarily mediated by AMPA/kainate and NMDA receptors, respectively.

Delta Wave and Alpha–Beta Oscillation are the Two Principal Components of Spindle Burst

Spindle bursts have been described as the principal pattern of cortical activity in rodents during the postnatal developmental period in various cortical regions (Khazipov et al. 2004; Hanganu et al. 2006; Minlebaev et al. 2007; Hanganu et al. 2007). Although the presence of a delta component in the spindle burst had been indicated, previous studies have mainly focused on it rapid oscillatory component, the short-living oscillation in alpha–beta frequency range. In the present study, using DC, and low-value high-pass filtered AC recordings we have revealed a robust delta component of spindle bursts. This slow component attained hundreds of microvolts in amplitude, and enveloped the alpha–beta oscillatory component. Robust delta components were not seen in pervious studies because they employed AC-coupled amplifiers with 1–3 Hz high-pass filters that severely compromised the delta waves, their amplitude and waveform (Fig. 1).

Several lines of evidence indicate that delta waves, together with the alpha–beta oscillation, are 2 component features of a single cortical event: 1) all spindle bursts, both spontaneous and sensory-evoked, contained both delta and alpha–beta oscillatory components; 2) there was a tight temporal and quantitative correlation between the power of alpha–beta oscillations and the time course and amplitude of delta waves; 3) both components had a similar depth profile and the location of the major sinks was in the dense cortical plate; 4) ionotropic glutamate receptors were involved in the generation of both components. Taken together, these results indicate that alpha–beta oscillations and delta waves are the 2 intimately linked elements of the spindle burst.

The results of the pharmacological analysis of the present and previous study suggest that the generation of spindle bursts in the neonatal barrel cortex is primarily a result of activation of synapses between glutamatergic cells. Interestingly, the relative contribution of AMPA/kainate and NMDA-Rs to the generation of the delta and alpha–beta oscillations is different. Alpha–beta oscillations mainly require AMPA/kainate receptors, and blockade of NMDA-Rs has no significant effect on this rapid oscillatory component. On the other hand, the delta wave is generated by both types of glutamate receptors, with a primarily contribution of NMDA-Rs. The differential contribution of the AMPA/kainate and NMDA-Rs to the 2 components of the spindle burst probably reflects a difference in the kinetics of the synaptic currents mediated by these receptors. AMPA-R mediated synaptic currents have fast, in the milliseconds range, rise- and decay times (see, e.g., Crair and Malenka 1995; Kidd and Isaac 1999; Khazipov et al. 2004), and therefore are ideally suited for synchronization of the rapid activities, such as alpha–beta oscillations. NMDA-R mediated synaptic currents have rise times in the range of 10 of milliseconds, and decay times of hundreds of milliseconds; they are particularly slow at the immature synapse (Carmignoto and Vicini 1992; Hestrin 1992; Monyer et al. 1994; Khazipov et al. 1995). The slow kinetics of NMDA-R mediated synaptic currents enables their powerful summation during rhythmic activation of synaptic inputs during spindle bursts. The high NMDA/AMPA ratio at the immature synapses is another important factor contributing to the increased contribution of NMDA-Rs to delta

wave (Crair and Malenka 1995; Durand et al. 1996; Isaac et al. 1997; Gasparini et al. 2000; Voronin et al. 2004).

NMDA-R–dependent patterns of activity in the developing cortical networks have been also described in vitro, including hippocampal giant depolarizing potentials (GDPs) (Ben-Ari et al. 1989) and associated calcium oscillations (Leinekugel et al. 1997), and neocortical bursting and oscillatory activity (LoTurco et al. 1991; Garaschuk et al. 2000; Arumugam et al. 2005; Kandler and Thiels 2005; Dupont et al. 2006). Interestingly, in the case of hippocampal GDPs, depolarizing GABA may facilitate activity of NMDA-Rs by attenuation of their voltage-dependent magnesium block (Khazipov et al. 1997; Leinekugel et al. 1997). In the neocortex in vivo however, GABA exerts an inhibitory action on the generation of delta wave. This is in agreement with our previous report of the inhibitory role of GABAergic interneurons in the compartmentalization of spindle bursts, presumably via a surround inhibition (Minlebaev et al. 2007). This is despite considerable evidence for depolarizing and excitatory actions of GABA in the immature neurons in the neocortex reported in vitro (Luhmann and Prince 1991; Yuste and Katz 1991; LoTurco et al. 1995; Owens et al. 1996; Owens et al. 1999; Dammerman et al. 2000; Garaschuk et al. 2000; Yamada et al. 2004; Ben Ari et al. 2007; Daw et al. 2007), which yet remains to be demonstrated in vivo. Because depolarizing GABA also exerts shunting action, we propose that the shunting inhibitory effects of GABA dominate during spindle bursts generation. These results are also in keeping with the plasticity changes induced in the developing barrel cortex by chronic treatment with the GABA(A) receptor agonist muscimol (Wallace et al. 2001). Because cortical GABAergic interneurons are interconnected via gap-junctions (Connors and Long 2004; Hestrin and Galarreta 2005), the inhibitory role of gap junctions in spindle-bursts generation that is suggested by the effects of gap-junction blockers may involve synchronization of interneurons via gap-junctions.

Human Correlates

With our description of a slow component of spindle bursts they appear similar to the human electrographic pattern of delta-brushes, which are expressed in human premature neonates during the second half of gestation (Dreyfus-Brisac and Larroche 1971; Anderson et al. 1985; Stockard-Pope et al. 1992; Lamblin et al. 1999; Scher2006; Milh et al. 2007). Like the rodent spindle burst, human delta-brushes are the dominant pattern of cortical activity during the comparable stages of the brain development. The remarkable similarities between these 2 patterns indicate that they are the same physiological phenomenon (Khazipov and Luhmann 2006). In a series of recent studies, it has been demonstrated that the slow component of delta-brushes is severely compromised in its amplitude and waveform by conventional >1 Hz high-pass AC-electroencephalographic recordings (Vanhatalo et al. 2002; Vanhatalo et al. 2005). DC recordings from premature neonates revealed robust, up to 800 μV, slow activity transients in association with the delta-brushes. Results of the present study are consistent with these observations, and finding a large slow component in both species provides further evidence for the homology between human delta-brushes and rodent spindle bursts. This also makes neonatal rodent an excellent model to study the mechanism and physiological roles for this unique activity pattern in the cortical development.

Physiological Roles for Delta Waves

The dual component spindle burst is expressed in the barrel cortex during the critical period of barrel formation (Crair and Malenka 1995; Katz and Shatz 1996; Fox et al. 1996; Feldman et al. 1998, 1999; Feldman 2001; Zhang and Poo 2001; Crowley and Katz 2002; Fox 2002; Katz and Crowley 2002; Cang et al. 2005; Hensch 2005; Feller and Scanziani 2005). NMDA-Rs are instrumental in activity-dependent plasticity during the critical period, and their pharmacological or genetic suppression results in anomalies of cortical development and functional deficits, most notably in the failure to form ordered somatotopic thalamocortical connections and the loss of synaptic plasticity (Schlaggar et al. 1993; Crair and Malenka 1995; Isaac et al. 1995a, 1997; Fox et al. 1996; Feldman et al. 1998, 1999; Iwasato et al. 2000; Fox 2002; Dagnew et al. 2003; Lee et al. 2005a, 2005b). Our results suggest that NMDA-dependent delta waves are generated by a massive summation of thalamocortical activity during spindle bursts thus providing a long time window for co-incident activation of cortical neurons by the thalamocortical cells. We propose that this physiological paradigm underlies the NMDA-R–dependent plasticity in developing thalamocortical synapses, including both potentiation/maintenance of the active during spindle-bursts synapses and depression/elimination of those synapses, which are less recruited by spindle bursts.

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Address correspondence to Roustem Khazipov, MD, PhD, INSERM U901/Inmed, 163 route de Luminy B.P. 13, 13273 Marseille, France. Email: khazipov@inmed.univ-mrs.fr.

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