Effects of Bicuculline Methiodide on Fast (>200 Hz) Electrical Oscillations in Rat Somatosensory Cortex

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Jones, Michael S. and Daniel S. Barth. Effects of bicuculline methiodide on fast (>200 Hz) electrical oscillations in rat somatosensory cortex. J Neurophysiol 88: 1016–1025, 2002; 10.1152/jn.00068.2002. Fast oscillatory activity (more than ~200 Hz) has been attracting increasing attention regarding its possible role in both normal brain function and epileptogenesis. Yet, its underlying cellular mechanism remains poorly understood. Our prior investigation of the phenomenon in rat somatosensory cortex indicated that fast oscillations result from repetitive synaptic activation of cortical pyramidal cells originating from GABAergic interneurons (Jones et al. 2000). To test this hypothesis, the effects of topical application of the γ-aminobutyric acid-A (GABA A ) antagonist bicuculline methiodide (BMI) on fast oscillations were examined. At subconvulsive concentrations (~10 μM), BMI application resulted in a pronounced enhancement of fast activity, in some trials doubling the number of oscillatory cycles evoked by whisker stimulation. The amplitude and frequency of fast activity were not affected by BMI in a statistically significant fashion. At higher concentrations, BMI application resulted in the emergence of recurring spontaneous slow-wave discharges resembling interictal spikes (IIS) and the eventual onset of seizure. High-pass filtering of the IIS revealed that a burst of fast oscillations accompanied the spontaneous discharge. This activity was present in both the pre- and postictal regimes, in which its morphology and spatial distribution were largely indistinguishable. These data indicate that fast cortical oscillations do not reflect GABAergic postsynaptic currents. An alternate account consistent with results observed to date is that this activity may instead arise from population spiking in pyramidal cells, possibly mediated by electrotonic coupling in a manner analogous to that underlying 200-Hz ripple in the hippocampus. Additionally, fast oscillations occur within spontaneous epileptiform discharges. However, at least under the present experimental conditions, they do not appear to be a reliable predictor of seizure onset nor an indicator of the seizure focus.

INTRODUCTION

The cortical response to an elementary sensory stimulus consists of a series of stereotyped cellular events which give rise to the familiar evoked potential (EP) complex recordable both intra- and extracranially. Although the large-amplitude components of the evoked potential are relatively slow, with dominant frequency of ~40 Hz, the EP also contains high-frequency activity. This is apparent as a series of small-amplitude deflections superimposed on the slow-wave EP components which, following high-pass filtering, are seen to result from a burst of fast oscillations, exhibiting a center frequency in excess of several hundred hertz (Curio et al. 1994a; Jones and Barth 1999b; Kandel and Buzsaki 1997).

Fast oscillatory activity has been attracting increasing interest concerning its potential role in normal and pathological brain function (Curio 2000; Traub et al. 2001). Somatosensory-evoked fast oscillations have been noninvasively investigated in humans with electroencephalographic (Cracco and Cracco 1976; Eisen et al. 1984; Maccabee et al. 1983; Yamada et al. 1984) and magnetoencephalographic (Curio et al. 1994a,b; Gobbelé et al. 1998; Hashimoto et al. 1996) recording, demonstrating that, similar to the slow-wave components of the somatosensory evoked potential (SEP), they are of cortical origin, exhibiting a somatotopic organization in the postcentral gyrus (Curio et al. 1997; Hashimoto et al. 1996). However, slow and fast components of the human SEP are differentially affected by sleep (Yamada et al. 1988) and stimulus parameters (Klostermann et al. 1999), suggesting that disparate cellular generators are responsible for these phenomena.

Our laboratory has investigated fast oscillations invasively in rat somatosensory cortex to identify its underlying cellular mechanism. This work has confirmed the cortical origin of fast oscillations, which exhibit a dipolar pattern in the lamina and propagate intracortically (Jones and Barth 1999b). Intracellular investigation showed that whisker-evoked burst firing in fast spiking (FS) cells is closely associated with fast oscillations present in the surface record (Jones et al. 2000). As FS cells correspond morphologically to smooth or sparsely spiny GABAergic interneurons (Kawaguchi 1993; McCormick et al. 1985), these results suggest that inhibitory interneurons may act as pacemakers of fast oscillations. Such a generator has been proposed for 600-Hz “sigma-bursts” observed in the human magnetoencephalogram (MEG) (Hashimoto et al. 1996), and analogous inhibitory neural circuitry is known to participate in 200-Hz “ripples” in the hippocampus (Buzsaki et al. 1992; Ylinen et al. 1995).

Conversely, a second finding of intracellular investigation was that the evoked suprathreshold response in many regular spiking units (presumably pyramidal cells) exhibits a periodicity similar to that of the simultaneously recorded fast oscillations (Jones et al. 2000), a feature also noted in extracellular recording of multi-unit activity (Kandel and Buzsaki 1997). Thus fast oscillations may arise from excitatory interactions within the cortical network, with pyramidal cells serving as

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both pre- and postsynaptic participants. This is supported at least indirectly by recent investigations in the hippocampus, indicating that high-frequency oscillations (\(>200\) Hz) termed “fast ripples” are produced by pathological increases in excitability within the developing epileptic focus (Bragin et al. 2000).

The purpose of the present study was to clarify the possible synaptic contributions to fast oscillations in rat somatosensory cortex. To this end, epicortical application of the \(\gamma\)-aminobutyric acid-A (GABA\(_A\)) receptor antagonist bicuculline methiodide (BMI) was used to effect gross blockade of fast inhibition in the cortical network. Low concentrations of BMI may be applied in this fashion without inducing seizure, which permits the effects of GABA\(_A\) antagonism on stimulus-evoked fast oscillations to be explored. Should fast oscillations directly reflect GABAergic postsynaptic currents driven by inhibitory interneurons, BMI should attenuate or eliminate this activity. At higher concentrations, topical application of BMI typically leads to ictus. Such a preparation provides the opportunity to study possible associations between fast oscillations and seizure onset in a simple model of neocortical epileptogenesis.

**METHODS**

**Surgery**

All procedures were performed in accordance with University of Colorado Institutional Animal Care and Use Committee guidelines for the humane use of laboratory animals in biological research. Adult male Sprague-Dawley rats (325–375 g) were anesthetized to surgical levels using intramuscular injections of ketamine HCl (100 mg/kg) and xylazine (25 mg/kg) and placed on a regulated heating pad. Anesthesia was subsequently maintained via continuous intramuscular administration of vehicle alone (control) are not presented. No change in the pH of the surface after removal of the surface array at the approximate focus of the averaged surface response. The laminar array was advanced until the top electrode was barely visible at the cortical surface and left in place 20 min before data collection was begun. Laminar and epipial potentials were referenced to a silver ball electrode secured over the contralateral frontal bone. Surface potentials were amplified (\(\times500\)), analog filtered (band-pass cutoff = -6 dB at 1–3000 Hz, roll-off = 5 dB/octave), and digitized at 10 kHz. Laminar potentials were preamplified using a \(\times10\) headstage and subsequently amplified (\(\times200\)), analog filtered, and digitized in the same fashion as surface potentials.

**Drug application**

Squares of filter paper (\(5 \times 5\) mm) were saturated with BMI (Sigma/RBI; \(\sim 10\) \(\mu\)M), mixed in 0.9% NaCl, applied to the surface of the cortex surrounding the laminar electrode array, and left in place throughout subsequent data collection. The saline vehicle was a physiological solution that is routinely used to moisten the cortex over the course of all of our experiments. For this reason, results of application of vehicle alone (control) are not presented. No change in the pH of this solution was detected following addition of BMI.

**Data collection and analysis**

Two hundred millisecond samples of the whisker-evoked response were recorded, with data from individual trials stored digitally for subsequent analysis. Fifty trials were collected prior to BMI application, 2 min after BMI application, and 30 min after wash. Trials that contained spontaneous discharges or excessive baseline activity or in which the animal was unresponsive were discarded.

The effects of BMI on the peak-to-peak amplitude, center frequency, and duration of evoked fast activity were quantified. Peak-to-peak amplitude of a given trial was defined as the difference between the maximum and minimum values of the high-pass filtered signal, computed for each channel and then averaged across all 16 channels of the laminar array. Center frequency was defined as the largest spectral peak above 200 Hz appearing in a 512-point fast Fourier transform (FFT) of the wide-band data centered on the P1 peak. Response duration was defined as the total time during which the rectified and smoothed high-frequency signal exceeded two times the SD of the prestimulus baseline (even if intervening portions of the response fell below this threshold) and was averaged across all channels. A number of alternate duration measures were examined, including surface-channel-only, maximum duration across all channels, and power-based measures defined using sliding FFT windows of various lengths, all of which gave qualitatively similar results. Data were pooled across animals and analyzed using a repeated-measures analysis of variance (ANOVA).

It should be noted that current source density analysis (CSD) was not performed in the present study. We have found that the laminar profile of fast oscillations exhibits a substantial amount of trial-to-trial variability, such that legitimate CSD analysis of this activity requires nontrivial extensions to the method. These issues distract from and are not critical to the salient points of the study, and as such, these CSD results are not included in the present report.
RESULTS

Pulse displacement of the vibrissae elicited a surface response with a single-amplitude focus presumably centered at the cortical representation of the stimulated vibrissae (Fig. 1C). The morphology of the evoked response was consistent with the stereotypical SEP biphasic waveform, with a surface-positive peak (P1) emerging ∼20-ms poststimulus, followed closely by a prominent surface-negative peak (N1). In addition to these slow-wave components, the surface response also displayed evidence of high-frequency activity. Power spectral density of averaged SEP data exhibited a prominent peak between 200 and 500 Hz (Fig. 1C; far right). Band-pass
filtering of the SEP within these frequencies extracted a burst of high-frequency oscillations from the SEP complex, \( \sim 25-50 \) \( \mu \)V in amplitude and with a center frequency of \( \sim 450 \) Hz.

Wide-band laminar potentials recorded from the amplitude focus of the surface response exhibited a distribution and morphology consistent with previous laminar studies of both the slow-wave and the fast oscillatory response in sensory cortex (Jones and Barth 1999b). The biphasic morphology of the surface-evoked potential was distinguishable in the top channel of the laminar array (Fig. 2B), reversing polarity at electrodes located in deep cortical lamina. High-frequency activity was apparent in most lamina as a series of small ripples superimposed on the underlying slow-wave components. Such ripples were also observed in the surface response; however, they are less apparent in averaged data such as that shown in Fig. 1C than in the individual trial data depicted in Fig. 2B. Fast activity extracted from the laminar wide-band data by band-pass filtering exhibited a dipolar profile (Fig. 2C), with complementary peaks of opposite polarity present for all major cycles in an oscillatory burst. The reversal point of this activity was in the middle cortical lamina and to first approximation appeared to be identical for all peaks.

Epicortical application of BMI had a rapid and dramatic effect on fast activity. The predominant change was an increase in the number of oscillatory cycles evoked by whisker stimulation, from the five to seven cycles typically observed under baseline conditions to as many as \( \sim 15 \) cycles within 2 min of BMI application. This was accompanied by changes in slow-wave components as well, including an increase in the overall amplitude of the SEP complex and a broadening of the P1 and N1 peaks (Fig. 3, inset). These effects were reversible, with both fast and slow activity returning to baseline 30 min following wash (Fig. 3, “wash”). Other features of fast activity did not appear to be affected by BMI. Notably, there was little change in amplitude or frequency, nor any apparent reorganization of its laminar distribution, although the latter was hard to quantify given the inherit variability of the spatiotemporal distribution of fast activity.

Statistical analysis confirmed the observations noted above. The duration of fast activity increased from a mean value of 43 ms in the baseline to 52 ms following application of BMI (\( P < 0.001; \) Fig. 4, left). No significant change was observed in amplitude (Fig. 4, center) or frequency (Fig. 4, right).

Higher concentrations of bicuculline used during surface mapping resulted in the appearance of spontaneous interictal spikes (IIS) within the first 1.0- to 6.0-min sampling epoch (Fig. 5C). Spontaneous IIS were similar to stimulus-evoked IIS and were characterized by an initial positive/negative slow-wave of approximately 50-ms duration (Fig. 5B, top trace) at the cortical surface. Digital high-pass filtering (200-500 Hz) of
due to differences in the concentration and spread of bicuculine. The initial slow positive wave of the IIS was earliest in the most caudal electrodes of the array and spread to the more rostral electrodes over a time period of 28 ms (Fig. 5D, left inset) or at a rate of ~125 μm/ms. The average rectified fast activity (Fig. 5C, right traces) closely followed the latency and spatial distribution of the slow-wave IIS complex and appeared to track the epileptiform discharge as it propagated through the cortex (Fig. 5D, right inset). Latency shifts of the positive amplitude peak of the IIS and rectified fast activity were positively correlated across electrodes in this epoch ($r = 0.85; n = 63, P < 0.01$), across all epochs in this animal ($r = 0.59; n = 945, P < 0.01$), and across animals ($r = 0.6140; n = 2457, P < 0.01$). A seizure occurred during 7.0- to 11.0-min post-bicuculline and precluded averaging the IIS. In the epoch immediately following this (Fig. 5D), the spatiotemporal pattern of both the IIS and the fast oscillations was little changed. The amplitudes of both slow and fast activity appeared slightly larger postictically, but this increase was insignificant compared with the amplitude variability throughout the 1-h recording session. However, changes in the amplitude of the IIS and fast oscillations across all 5-min epochs in this animal were highly correlated ($r = 0.75; n = 15, P < 0.01$) as they were across animals ($r = 0.68; n = 39, P < 0.01$). Recordings during seizures were not analyzed because of the possibility of movement artifact in these unparalyzed animals. However, in none of the five seizures recorded was there evidence for a change in fast oscillatory activity independent of the slow-waves of the IIS complex just preceding seizure onset (Fig. 5E).

**Discussion**

Two principal results emerge from these data. 1) Epicortical application of BMI enhances stimulus-evoked high-frequency oscillations, causing a pronounced increase in the number of oscillatory cycles evoked by whisker stimulation. The amplitude and frequency of this activity was not affected by BMI in a statistically significant fashion. 2) High-frequency oscillations occur within spontaneous epileptiform discharges induced by BMI. Such spontaneous bursts were observed when using BMI at concentrations sufficient to lead to seizure. However, at least under the present experimental conditions, fast oscillations do not appear to be a reliable indicator of the interictal-to-ictal transition. The implication of these results will be discussed in terms of the cellular generator of this activity and the possible role high-frequency oscillations may play in epileptiform discharge.

The fast oscillations reported in the present study are the dominant high-frequency activity occurring in rat somatosensory cortex and have been observed under differing stimulation, recording, and anesthesia conditions (Jones and Barth 1999b; Jones et al. 2000). However, these oscillations vary in frequency by ~25% across studies, suggesting that frequency is not a reliable defining feature. Additionally, fast oscillations may be a heterogeneous phenomenon. Two co-occurring fast oscillatory phenomenon, segregated into frequency bands of 200–400 and 400–600 Hz, have been observed (Jones et al. 2000), with activity in the lower band occurring at the earliest poststimulus latencies. However, this component was not evident in an earlier study (Jones and Barth 1999b) nor in the present data. Association of the slower component with the P1...
peak suggests that it may partially reflect the sequential laminar activation pattern that dominates the cortical-evoked response (Barth and Di 1990). Additionally, this component may reflect a synchronized thalamocortical volley, analogous to that recently demonstrated in the piglet (Ikeda et al. 2002). While the lability of the slower component makes its neural mechanism difficult to establish, the fast oscillations reported here are robust and have been consistently observed under a variety of experimental conditions.

Replicating results of our previous studies (Jones and Barth 1999a; Jones et al. 2000), the laminar profile of fast oscillations exhibits a dipolar configuration. As shown in Fig. 2C, each of the major surface peaks of a given oscillatory burst are aligned with a peak of opposite polarity occurring in deep lamina. This dipolar pattern indicates that the cellular currents underlying fast oscillations are largely constrained in the vertical direction. Such currents will arise as a result of synchronized activity in cellular elements which similarly exhibit a prominent vertical orientation, appearing as the extracellular passive return currents that are established to satisfy current continuity requirements (Hubbard et al. 1969; Johnston and Wu 1997). The neuronal element that is immediately suggested by these considerations is the cortical pyramidal cell, with its long vertically oriented apical dendrite providing an optimal cellular substrate for generating elongated large-amplitude dipolar field potentials.

Previous intracellular recordings demonstrate that whisker-evoked burst firing in fast spiking units (presumably inhibitory interneurons) is closely associated with simultaneously recorded fast oscillatory activity (Jones et al. 2000). This, in addition to their dipolar laminar profile, suggests that fast oscillations may reflect a population inhibitory postsynaptic potential (IPSP) arising in field potentials as FS spike bursts impinge on their pyramidal cell targets. However, the present results clearly do not support this model. Although bicuculline is known to exert a number of nonsynaptic effects (Heyer et al. 1982; Olsen et al. 1976), the results of BMI application observed presently are wholly consistent with its established action as a GABA<sub>A</sub>-receptor antagonist. Topical application of BMI increased cortical excitability. This is supported not only by the emergence of spontaneous discharges and, in some instances, seizure following drug application, but also by changes induced in SEP morphology. BMI both increased the amplitude and accelerated the onset of the SEP, as well as broadened both P1 and N1 peaks, events known to be associated with excitatory cortical processes (Brailowsky and Knight 1984; Zemon et al. 1980). Yet, fast activity was prolonged but otherwise unaltered by application of BMI. Amplitude remained unchanged (Fig. 4), which would not be expected if the synaptic currents underlying the phenomenon were blocked. There was no overt change in morphology or frequency, as might be expected if the dynamics of this activity were con-
trolled by GABA_A processes. Last, there was no apparent reorganization of its laminar distribution that might suggest a nonuniform perfusion of BMI that may have spared deep GABA_A currents. The spread of bicuculline or its effective concentration at the receptor site is not known. However, the effects of BMI were qualitatively similar for all concentrations used in the study. From brief application of subconvulsive doses to prolonged exposure to sufficient quantities of BMI to induce seizure, a singular salient result is observed: fast oscillations cannot be extinguished by application of bicuculline.
This result strongly suggests that fast oscillations do not reflect population IPSPs.

A possible alternative account of fast oscillations is that they may reflect population excitatory postsynaptic potentials (EPSPs). There is substantial recurrent excitation within the cortical network, with a large fraction of asymmetric synapses found on a given pyramidal cell originating from other pyramidal cells (Braitenberg and Schütz 1998; White 1989). Our intracellular investigations have uncovered a subset of regular spiking units (presumably pyramidal cells) that exhibit suprathereshold responses at preferred latencies defined by successive cycles of fast oscillatory activity (Jones et al. 2000). Thus pyramidal cells may serve as both pre- and postsynaptic elements in the fast oscillatory response, with synchronized population firing imposing potent postsynaptic currents that regenerate the next cycle of fast activity and ramify in field potentials as one peak of the fast oscillatory burst. Yet, several considerations cast doubt on the efficacy of recurrent EPSPs to synchronize activity at the millisecond time scales required to generate coherent fast oscillatory field potentials. These include the time course of EPSPs, the nonproximal termination of recurrent collaterals, and a substantial incidence of synaptic transmission failure (see e.g., Miles and Wong 1986 and references therein). Additionally, computational studies of 200-Hz oscillations in the hippocampus indicate that high-frequency synchronization cannot be achieved via chemical synapses (Traub et al. 1999).

These arguments suggest a third possibility, that fast oscillations may reflect population spikes in cortical pyramidal cells. This hypothesis is consistent with our intracellular results, which noted that whisker-evoked spiking in a subset of RS units occurs at preferred latencies defined by the fast oscillatory burst (Jones et al. 2000). Extracellular currents associated with pyramidal cell action potentials are expected to give rise to vertically oriented field potential dipoles (Rall 1962). When synchronized across a sufficiently large cell population, such activity could contribute coherent small-amplitude oscillations against a background of larger slow-wave SEP components, the latter likely reflecting excitative chemical synaptic interactions (Barth and Di 1990). Such a combination of slow-wave and fast oscillatory activity has been observed in the hippocampus, in which 200-Hz ripples are superimposed on field potential sharp waves (Buzsáki et al. 1992; Ylinen et al. 1995). The study of the electrogenesis of 200-Hz activity has benefited from its persistence in the hippocampal slice (Draguhn et al. 1998) and is thought to emerge from repetitive population spikes in a network of electrotonically coupled pyramidal cells, likely via axonal gap junctions (Schmitz et al. 2001; Traub et al. 1994). These oscillations are not dependent on chemical synaptic transmission and are abolished by gap junction blockers such as halothane, an effect that is also observed in the intact animal (Ylinen et al. 1995).

Fast oscillations reported here may therefore reflect a phenomenon analogous to hippocampal ripple, operating in cortex. The preferred spiking latencies exhibited by cortical RS units are similarly observed in hippocampal pyramidal cells, which tend to fire action potentials only on one or some cycles of a given oscillatory burst, if they fire at all (Buzsáki et al. 1992). Additionally, there is evidence that cortical pyramidal cells may be coupled by gap junctions (Gutnick and Prince 1981). Last, computational models of ripple reproduce the correlated spike bursting in inhibitory interneurons we observe as a consequence of phasic drive from the pyramidal cell network (Traub and Bibbig 2000; Traub et al. 2001; see also Lewis and Rinzel 2000). This model is thus consistent with our previous intracellular results and the present observation that BMI fails to extinguish fast cortical oscillations. There may be contributions from both population IPSPs and population spikes in the hippocampus or in the undrugged cortex, but synchronized population spiking appears to be the dominant contributor in cortex under the present experimental conditions.

The analogy between fast oscillations in cortex and hippocampus may also be extended to their putative role in epileptogenesis. Fast ripples are associated with epileptiform discharge in both in vitro (Schwartzkroin and Prince 1977, 1978; Traub et al. 2001; Wong and Traub 1983) and in vivo models of hippocampal seizures (Bragin et al. 1999b,c, 2000), and with human temporal lobe epilepsy (Bragin et al. 1999a,b), possibly reflecting synchronized population spikes as noted by Dudek and co-workers (Buckmaster and Dudek 1997, 1999; Hellier et al. 1999; Patrylo et al. 1999). Fast oscillations or ripples in both cortex and hippocampus are above 200 Hz and superimposed on the rising limb of the depolarizing slow wave of the IIS. Both are associated with spontaneous IIS as well as stimulus-triggered IIS. Finally, both oscillatory phenomena are linked to
decreased inhibition, suggesting excitatory interactions between principal neurons.

Yet, there are differences between cortical fast oscillations and hippocampal fast ripples that make their direct comparison problematic. While fast ripples are usually superimposed on the IIS, they may also be spatially and temporally dissociated (Bragin et al. 1999b). IIS recorded outside the epileptogenic lesion in the rat kainate model have no accompanying fast ripples, and fast ripples may be recorded in the vicinity of the lesion with no clear IIS slow-wave. In contrast, both stimulus-triggered and spontaneous fast oscillations recorded in somatosensory cortex are closely associated with the IIS slow-wave and do not occur independently. Fast oscillations and IIS display a similar spatial distribution and propagate in tandem through the cortex. However, the full extent of the epileptic focus was not mapped in the present study, so potential differences in the spatial distributions of fast oscillations and the IIS may have gone undetected. Finally, while cortical fast oscillations during IIS appear as a simple prolongation of the normal response to sensory stimulation, fast ripples are distinctly associated with an epileptic lesion and cannot be recorded in normal hippocampus.

While cortical fast oscillations may not be directly comparable to the hippocampal fast ripples of temporal lobe epilepsy, the association between normal sensory-evoked fast oscillations and those occurring during IIS suggests a unique role these phenomena could play in cortical epileptogenesis. We have proposed that fast oscillations facilitate precise intra- and inter-columnar synchronization during multi-vibrissa-evoked responses (Jones and Barth 1999a), a phenomenon that may underlie somatosensory pattern detection or texture discrimination in the rat. Thus cellular circuitry responsible for synchronization required of normal sensory processing may be exploited in pathological states of decreased inhibition to trigger epileptiform discharge in abnormal cortex and/or to propagate these discharges in normal cortex surrounding the epileptic focus. In the human cortex, fast oscillations have been shown to characterize both the sensory evoked response (Curio et al. 1994a,b, 1997; Gobbelé et al. 1998; Green et al. 1986; Hashimoto et al. 1996; Maccabee et al. 1983; Yamada et al. 1984, 1988) and the abnormal activity preceding seizure onset (Traub et al. 2001). Thus continued study of the phenomenon may not only contribute to an understanding of seizure initiation and propagation, but also help elucidate fundamental mechanisms of information processing in the human neocortex.

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