Enhanced Propagation of Epileptiform Activity Through the Kindled Dentate Gyrus

J. BEHR, K. J. LYSON, AND I. MODY
Departments of Neurology and Physiology, Reed Neurological Research Center, UCLA School of Medicine, Los Angeles, California 90095-1769

Behr, J., K. J. Lyson, and I. Mody. Enhanced propagation of epileptiform activity through the kindled dentate gyrus. J. Neurophysiol. 79: 1726–1732, 1998. Extracellular recordings were performed in combined hippocampal-entorhinal cortex (HC-EC) slices obtained from control and commissural kindled rats to investigate the propagation of epileptiform activity from the entorhinal cortex (EC) to the hippocampus (HC) after chronic epilepsy. Lowering extracellular Mg2+ concentration in control slices induced epileptiform activity consisting of spontaneous epileptiform bursts in area CA3 and of electrographic seizures in the EC. In contrast, the CA3 region of HC-EC slices obtained from kindled rats displayed significantly longer lasting epileptiform bursts and electrographic seizures. The electrographic seizures that were absent in controls propagated from the EC because disconnecting the HC from the EC stopped their occurrence in the CA3, whereas epileptiform bursts persisted with an unaltered pattern and frequency. Thus the area CA3 is affected by kindling and contributes to the spread of epileptiform activity within the EC-HC complex. We developed a method to induce focal epileptiform activity in the EC by locally perfusing the γ-aminobutyric acid-A (GABA) antagonist bicuculine (50 mM) in 10 mM KCl containing artificial cerebrospinal fluid. This method enabled us to investigate the propagation of epileptiform discharges from the disinhibited EC to the DG without affecting the DG with the epileptogenic medium. We show here that kindling facilitates the propagation of epileptiform activity through the DG. These data are consistent with the normal function of the DG as a filter limiting the spread of epileptiform activity within the HC-EC complex. This gating mechanism breaks down after chronic epilepsy induced by kindling.

INTRODUCTION

Numerous studies investigated alterations in the dentate gyrus (DG) during epileptogenesis (for reviews, see Ribak et al. 1992; Schwartzkroin 1993). These alterations seem to play a major role in the propagation of epileptiform activity from the entorhinal cortex (EC) to the hippocampus (HC). Spontaneous epileptiform activity in the HC-EC slice preparation can be induced by lowering extracellular Mg2+ concentration (Heinemann and Jones 1990; Jones and Heinemann 1988; Walther et al. 1986). Areas CA3 and CA1 exhibit epileptiform bursts that are quite stable over time (Leschinger et al. 1993; Mody et al. 1987). Longer lasting events cannot be observed in 400- to 450-μm-thick slices (Dreier and Heinemann 1991), although such events have been reported to occur occasionally in 625-μm slices with decreasing frequency in older animals (Anderson et al. 1986). In contrast, the electrical activity induced by low Mg2+ in the EC and the subiculum consists of electrographic seizures (Jones and Heinemann 1988; Walther et al. 1986), which develop into epileptiform bursts (Dreier and Heinemann 1991). In spite of the well-preserved fiber connectivity between the EC and the DG in slice preparations, electrographic seizures generated in the EC do not readily recruit the DG (Heinemann et al. 1990; Jones and Lambert 1990; Lambert and Jones 1989; Walther et al. 1986) and are not transmitted to hippocampal areas CA3 and CA1 (Dreier and Heinemann 1991). Thus the DG was suggested to function as a filter preventing the spread of epileptiform activity to the HC (Heinemann et al. 1992; Lothman et al. 1992). In contrast to controls, in HC-EC slices obtained from kindled rats, electrographic seizures generated in the EC spread to the DG and to areas CA3 and CA1 (Behr et al. 1996). Kindling seems to facilitate the propagation of epileptiform activity through the HC-EC slice and appears to alter the filtering function of the DG. However, all previous in vitro studies have resorted to perfusing the epileptogenic medium over the whole extent of the slice preparation. Therefore the contribution of the DG to seizure propagation always was assessed in the presence of an epileptogenic medium, precluding the measurement of its unperturbed function. In superfused brain slice preparations where many neurons are connected synaptically, it is difficult to single out the effect of a particular treatment on a specific neuronal population. Local perfusion systems (Engert and Bonhoeffer 1997; Veselovsky et al. 1996; West et al. 1992) have been used successfully to modify the extracellular environment of a restricted slice region. Yet no studies exist on the effects of various compounds administered locally on a relatively distant synaptically connected brain area. To examine the spread of epileptiform activity, we developed a local perfusion system that allowed us to induce focal epileptiform activity in the EC without altering the physiology of the DG. We monitored the propagation of stimulus-evoked responses and of spontaneous epileptiform events from the disinhibited EC to the DG in control and kindled rat slices. Moreover, we investigated the contribution of the hippocampal area CA3 to the spread of epileptiform activity induced by the EC in kindled animals.

METHODS

The experiments were performed on 21 kindled and 21 control horizontal slices containing the EC, the subiculum, and the hippocampal formation obtained from 30 implanted 450- to 600-g adult Wistar rats. Bipolar stainless steel electrodes were implanted under pentobarbital sodium anesthesia (75 mg/kg ip) into the midline hippocampal commissures (AP, −1.8; L, 0.0; V, 4.2) (Paxinos...
and Watson 1986). Commissural stimulation was employed to accelerate the uniform and bilateral development of stage 5 seizures. After a postsurgical recovery period of 7 days, 16 animals were stimulated daily through the implanted electrode with a train of biphasic 150-μA pulses at 60 Hz for 1 s. The behavioral changes induced by the kindling process were scored according to the scale of Racine (1972). The remaining 14 unstimulated animals were used as controls (sham-controls). Animals were stimulated until ≥15 consecutive stage 5 seizures were obtained. Three weeks after the last seizure, the animals were decapitated under pentobarbital sodium (75 mg/kg ip) anesthesia, and the brains were removed. The brains were cooled for ≥1 min in 4°C artificial cerebrospinal fluid (ACSF) containing (in mM) 126 NaCl, 1.25 NaH₂PO₄, 26 NaHCO₃, 2.5 KCl, 2 CaCl₂, 2 MgCl₂, and 10 d-glucose at a pH of 7.4. Horizontal 400-μm-thick slices were prepared using a Lancer Series 1000 vibratome (Staley et al. 1992). Before recordings, the slices were incubated at 32°C for 1–6 h in a 300 ml storage chamber filled with ACSF and continuously bubbled with a mixture of 95% O₂-5% CO₂. To induce epileptiform activity, either MgCl₂ was omitted from the ACSF or a restricted region of the slice was perfused with 50 μM bicuculline (BMI) in 10 mM KCl containing ACSF. Preliminary experiments have shown that local perfusion of BMI or KCl alone were not as reliable as both agents together in altering the activity in the EC.

The independent ACSF perfusion over a restricted region of the slice was achieved by using a cannula prepared from 1.55-mm-diam theta glass glued with acrylic cement to two 27-gauge stainless steel needles and two pieces of 30-gauge Teflon tubing connected to a peristaltic push-pull pump. The flow rate was set to 0.5 ml/min. The cannula was placed over the slice in the EC downstream of the main ACSF flow from the DG. A relatively high ACSF flow rate (2–3 ml/min) was necessary to prevent diffusion of the perfusate back to the DG. Thus a region of continuous and local flow was formed above a restricted area of the EC that occasionally was visualized by including methylene blue or phenol red in the local perfusion medium (Fig. 1).

Recordings of antidromic (EC) and orthodromic (DG) responses were done using standard extracellular recording pipettes in layers II–III of the EC and the DG granule cell layer, respectively. The stimulating electrode was placed onto the perforant path fibers connecting the two regions. Before each experiment, the flow over a restricted region of the EC was adjusted and controlled by ensuring that the evoked DG response remained unchanged while perfusing the EC for >10 min with an ACSF containing 5 mM kynurenic acid, a nonselective glutamate receptor antagonist (Fig. 1). A block of the synaptic, but not of the antidiromic, component in the EC and an unaltered orthodromic field potential in the DG was considered to indicate the proper placement of the local perfusion system providing an independent push-pull flow restricted to a portion of the EC. Subsequently, a 20-min local wash with ACSF over the EC allowed the slice to fully recover. The local EC perfusion then was switched to an ACSF containing 50 μM BMI and 10 mM KCl to induce epileptiform activity in a restricted region of the EC and to observe its propagation to the DG.

Recordings of slow field potentials were performed with ACSF-filled microelectrodes. Signals were filtered at 3 kHz, sampled at 10 kHz, and collected using a DT2821 A/D interface. Data are expressed as means ± SE and statistical comparisons were done by applying Student’s t-test (Origin 4.1, Microcal), or a χ²-test for determining differences between the fraction of total slices. Significance level was set to P < 0.05.

RESULTS

Lowering the extracellular Mg²⁺ concentration in the ACSF induced different patterns of epileptiform activity in the dentate gyrus (DG) [Fig. 1]. To induce DS, the ACSF containing 5 mM kynurenic acid for 10 min. If this treatment did not reduce the evoked excitatory postsynaptic potentials (EPSPs) recorded in the DG, the local perfusion was judged to be restricted to the EC.

FIG. 1. Schematic diagram of the local entorhinal cortex perfusion in the combined hippocampal-entorhinal cortex slice. One cannula each was inserted into the 2 barrels of the theta-glass capillary. Cannulae were connected to a push-pull pump. Tip of the capillary was lowered into layer III of the medial entorhinal cortex (mEC) in the vicinity of a recording electrode (R1). A relatively high flow rate (2–3 ml/min) in the direction indicated →, away from the dentate gyrus (DG), was necessary to prevent diffusion of the perfusate to the DG where a second recording electrode (R2) was used to monitor electrical activity. A stimulating electrode (S) was placed in the perforant path to antidromically and orthodromically activate entorhinal cortex (EC) and DG neurons, respectively. Occasionally, the extent of the local flow was monitored by including a dye (phenol red or methylene blue) in the local perfusate. pp, perforant path; mf, mossy fibers; Sch, Schaffer collaterals; alv, alveus; CA3, area CA3; CA1, area CA1; SUB, subiculum. Bottom: in each recording session, before any experimental manipulations were started, the restricted nature of the local EC perfusion was ensured by first perfusing an artificial cerebrospinal fluid (ACSF) containing 5 mM kynurenic acid for 10 min. If this treatment did not reduce the evoked excitatory postsynaptic potentials (EPSPs) recorded in the DG, the local perfusion was judged to be restricted to the EC.
HC-EC slices. In the EC of control slices, 30–60 min after lowering Mg\(^{2+}\), spontaneous electrographic seizures could be observed lasting between 5 and 67 s (36 ± 6.8 s, \(n = 10\); Fig. 2A, top left). In area CA3, the electrical activity consisted of epileptiform bursts with a mean duration of 1.1 ± 0.2 s and a frequency of 0.05–0.27 s\(^{-1}\) (\(n = 11\)) (Fig. 2A, top right). After lowering the Mg\(^{2+}\), the epileptiform bursts started at the same time as the electrographic seizures in the EC. In 4 of 13 control HC-EC slices, electrographic seizures also occurred in the DG and the CA3 region with a duration of 42.5 ± 4.9 s.

The characteristics of the early epileptiform activity in combined HC-EC slices of kindled rats are shown in Fig. 2A (bottom). Within 20–40 min of lowering the extracellular Mg\(^{2+}\), the EC generated electrographic seizures similar to those recorded in slices of control rats. The electrographic seizures lasted between 11 and 29 s and had a mean duration of 20 ± 3.7 s (\(n = 4\)), not significantly different from those recorded in controls (\(P = 0.18\)). In contrast to controls, in HC-EC slices of kindled rats, the epileptiform bursts in the CA3 region lasted significantly longer and had secondary discharges with a mean duration of 2.6 ± 0.3 s (\(P < 0.01\); \(n = 8\)). In kindled slices, area CA3 also was recruited into the electrographic seizures. The field potentials recorded in the CA3 region resembled the duration of those recorded in the EC, lasting between 9 and 43 s with a mean duration of 22.2 ± 3.1 s (\(n = 12\)) (Fig. 2B, top; 2 traces were recorded in different experiments). They were significantly shorter compared with the electrographic seizures of 4 of 13 controls that propagated to area CA3, indicating that in kindled slices even short electrographic seizures pass through the DG (\(P < 0.05\)).

To examine whether the electrographic seizures propagated from the EC, we used razor blade cuts to disconnect the EC from the DG and area CA1 from the subiculum. Figure 2B shows a schematic diagram of the transverse cuts. As expected, electrographic seizures immediately stopped after severing the perforant path (Fig. 2B, bottom left). However, epileptiform bursts lasting 1–4 s still could be detected, indicating the capacity of area CA3 to generate significantly longer epileptiform bursts in kindled slices than in controls. In three additional kindled slices, we disconnected area CA1 from the subiculum to rule out the possibility that the failure of electrographic seizures in area CA3 after perforant path transection resulted from the disconnection of the HC-EC loop. The cuts between area CA1 and the subiculum did not alter the propagation of electrographic seizures from the EC to area CA3 (Fig. 2B, bottom right).

The most common means of inducing epileptiform activity in vitro are to use \(\gamma\)-aminobutyric acid (GABA) antagonists (Schwartzkroin and Prince 1977, 1978), K\(^{+}\)-channel blockers (Schwartzkroin and Prince 1980), low extracellular Ca\(^{2+}\) (Jefferys and Haas 1982; Konnerth et al. 1986; Yaari et al. 1983) or Mg\(^{2+}\) (Anderson et al. 1986; Mody et al. 1987) or high extracellular K\(^{+}\) (Chamberlin and Dingledine 1988; Traynelis and Dingledine 1988). In all of these models, the whole brain slice is exposed to the agent that induces the epileptiform activity. Such experimental arrangement would preclude establishing whether the kindled DG may prevent the propagation of epileptiform events from the EC.
to the HC under physiological conditions. To avoid any change in the physiology of the DG while inducing epileptiform activity in the EC, a local perfusion system was developed to investigate the propagation of epileptiform activity through the control and kindled DG (Fig. 1; see METHODS).

We first compared perforant path evoked responses in the DG of control and kindled animals. In control slices, local disinhibition of the EC resulted in small and nonsignificant increases in evoked activity in the DG. In contrast, in slices obtained from kindled animals, we recorded a significant increase in the perforant path-evoked field potentials in the DG. The examples in Fig. 3A illustrate two superimposed traces recorded in the granule cell layer of a control and a kindled DG during local ACSF or BMI + KCl perfusions restricted to the EC. As no epileptogenic agent (BMI + KCl) was present in the DG, these findings are consistent with an enhanced excitability of the DG after disinhibition in the EC of kindled animals.

To quantify epileptiform activity in extracellular recordings, we employed the measurement of the “coastline index,” originally introduced by Dingledine et al. (1986). To obtain the coastline index, the total (dot-to-dot) length of the digitized traces was measured for 50 ms after the stimulus. To assess the enhancement of this index in the EC as well as in the DG after local disinhibition of the EC, we divided the numerical value of each index obtained in BMI + KCl by that recorded in ACSF. The ratios then were compared between kindled and control animals (Fig. 3B). The ratios observed in the DG showed a significantly larger increase in kindled slices, in spite of the lack of diffusion of BMI + KCl to this region. Although in control animals the local BMI + KCl increased the coastline of the antidromically evoked EC responses (ratio ~1.8), there was no significant change in the EC of kindled preparations (ratio ~1.1). This difference might be attributed to the already prolonged EC responses recorded in ACSF in kindled slices. Thus application of BMI + KCl lead to no further increase in the excitability of the kindled EC. It is also possible that extracellular recordings do not provide the required resolution to measure this small enhancement. The “throughput index” of the DG, calculated by dividing the ratios for the DG with those in the EC was 100% larger in kindled slices (n = 4–6 per bar; P < 0.05). These data demonstrate facilitated propagation of epileptiform activity through the DG in kindled preparations.

After prolonged (>10 min) local perfusions of the EC with BMI + KCl containing ACSF, we recorded spontaneous epileptiform activity in the disinhibited EC in three of eight control and nine of nine kindled HC-EC slices. The relative proportions are significantly different at P < 0.001 (x^2-test). The activity consisted of epileptiform bursts, but electrographic seizures comparable with those after lowering extracellular Mg^2+ in the whole slice could not be recorded.

We compared the propagation of spontaneous epileptiform activity to the DG in slices obtained from control and kindled animals. In control HC-EC slices, we did not record any propagated interictal events in the DG. In contrast, in seven of nine slices obtained from kindled rats, the DG participated strongly in interictal discharges (Fig. 4A). Figure 4B demonstrates simultaneous recordings of spontaneous epileptiform activity in the EC and the DG of kindled slices after local (EC) perfusion of BMI + KCl. The boxed traces (Fig. 4A, left) are shown on an expanded timescale on right to demonstrate the earlier timing of spontaneous events in the EC relative to the DG.

**DISCUSSION**

We investigated the impact of kindling-induced alterations in the DG and area CA3 on the propagation of epileptiform activity in combined HC-EC slices. After chronic epilepsy, the epileptiform activity generated in the EC propagated more easily to the DG and area CA3.

**FIG. 3.** A: superimposed traces of stimulus evoked responses recorded in the granule cell layer of a control and kindled DG during local (EC) perfusion with ACSF and with the γ-aminobutyric acid-A (GABA_A) receptor antagonist bicuculline (BMI; 50 μM) dissolved in 10 mM KCl containing ACSF. Local perfusion of the disinhibitory medium in slices obtained from implanted and sham-stimulated control animals showed only small increases in evoked activity in the DG. In contrast, in kindled slices, it resulted in a significant increase in epileptiform activity localized to the DG. B: we measured the “coastline index” (the total dot-to-dot length of the digitized traces during a 50-ms period after the stimulus) to quantitate the BMI + KCl-induced epileptiform activity in extracellular recordings. Histogram demonstrates changes in the recorded coastline index in control and kindled preparations. Ordinate shows the ratio obtained by dividing the value of the index obtained in BMI + KCl by that recorded in ACSF (i.e., the enhancement of the index by local perfusion of BMI + KCl in the EC). Note the large increase in the DG ratios in the kindled preparations. Significant difference in the EC ratios of kindled and control animals might result from the already enhanced EC responses recorded in ACSF in kindled slices. Thus addition of BMI + KCl led to no further increases in the excitability of the kindled EC. Ratios of the changes in the DG vs. those in the EC are shown in the DG/EC bars. The relative change was significantly larger in kindled preparations. Significant differences between kindled and control preparations are marked (* n = 4–6 per bar; P < 0.05).
Lowering the extracellular Mg\(^{2+}\) concentration generates epileptiform bursts in the CA3 area (Dreier and Heinemann 1991; Leschinger et al. 1993; Mody et al. 1987). Similarly, a low Mg\(^{2+}\) concentration results in repetitive firing of CA3 pyramidal cells in response to synaptic activation (Coan and Collingridge 1985; Herron et al. 1985) attributed to the abundant recurrent excitatory circuits (Johnston and Brown 1981; MacVicar and Dudek 1980; Miles and Wong 1986; Miles et al. 1984). Moreover, the ability of the CA3 pyramidal cells to generate intrinsic bursts may support epileptiform activity in this region (Miles and Wong 1983; Miles et al. 1991). Kindling significantly increased the duration of the epileptiform bursts. Furthermore, electrographic seizures restricted to the subiculum and the EC (Behr et al. 1996; Dreier and Heinemann 1991; Leschinger et al. 1993) in controls, were recorded in area CA3 of kindled preparations. The sensitivity of electrographic seizures in area CA3 to disconnecting the HC from the EC are consistent with the idea that electrographic seizures were propagated from the EC. Thus the hypothesis that kindling enables area CA3, at least in the slice preparation, to generate electrographic seizures without entorhinal epileptiform input can be ruled out. However, area CA3 appears to be affected by local alterations after kindling as epileptiform bursts were lengthened significantly compared with controls. Therefore, electrographic seizures that pass through the DG apparently spread to an altered and epilepsy-prone CA3 area that may support their propagation through the HC.

By using a method to induce local disinhibition in the EC, we have shown the spread of epileptiform activity to result mainly from kindling induced alterations of the DG. After extensive experimentation with several methods including grease-gap, the local push-pull cannula positioned downstream of the main ACSF flow proved to be most effective in producing a restricted local perfusion of the EC without any diffusion to the synaptically connected DG. In contrast to conventional methods, the transmission from the disinhibited EC and the spread of epileptiform activity toward the DG could be recorded without the target structure being affected by the epileptogenic agent.

The spontaneous epileptiform activity induced in the disinhibited EC propagated more easily through the DG in kindled animals than in controls. These data are consistent with an enhanced excitability of the kindled DG, which may no longer function as a filter to prevent the spread of epileptiform activity from the EC to the HC (Heinemann et al. 1992; Lothman et al. 1992). Both single cellular and neuronal network alterations may be responsible for the loss of this filter function, leading to a larger ease of seizure propagation through the kindled DG.

At the cellular level, changes in the glutamatergic system appear to result in a persistent increase in excitability and in the facilitated propagation of epileptiform activity. Non-NMDA receptors clearly are involved in the development of kindled seizures (Meldrum et al. 1992; Slevin et al. 1986). Kamphuis et al. (1994) showed kindling to be accompanied by an increased expression of the flp variant of GluR-A, -B, and -C mRNAs in DG cells 24 h after the last seizure. However, in the long term, only the GluR-A flp mRNA was enhanced. The NMDA subtype of glutamate receptor contributes significantly to epileptogenesis. Kindling-induced epilepsy and the associated mossy fiber sprouting depend on the activation of this receptor type (McNamara et al. 1990; Sutula et al. 1996). Moreover, the activation characteristics of NMDA receptors are altered (Köhrl et al. 1993; Mody and Heinemann 1987; Mody et al. 1988), resulting in persistent changes in the excitability of individual kindled neurons. Paradoxically, the function of the GABAergic system seems to be increased in the DG after kindling (Oliver and Miller 1985; Tuff et al. 1983). This may stem from an increased excitatory input onto GABAergic neurons, an increased quantal size of inhibitory postsynaptic currents, and a reduced presynaptic autoinhibition of GABA release (Buhl et al. 1996; Otis and Mody 1993). Yet, the enhanced activity of GABAergic synapses should not be considered synonymous with an augmented inhibition. Enlarged IPSPs

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**FIG. 4.** Propagation of epileptiform activity from the EC to DG in slices prepared from control and kindled animals. **A:** spontaneous epileptiform activity was induced in the EC of 3 of 8 control and 9 of 9 kindled slices after prolonged (>10 min) local (EC) perfusion of BMI + KCl (see text for details). Although in control HC-EC slices no propagated activity was recorded in the DG, in 7 of 9 kindled slices, the DG participated in interictal discharges. **B:** simultaneous recordings of spontaneous epileptiform activity in the EC and the DG of kindled slices after local (EC) perfusion of BMI + KCl. **Left:** boxed traces shown on an expanded time scale on the **right** to demonstrate the earlier timing of spontaneous events in the EC relative to the DG.
may actually underlie an increased synchrony of the principal cells (Cobb et al. 1995).

At the network level, previous studies described alterations in the synaptic transfer from the EC to the HC in kindled slices (Mody and Heinemann 1987; Mody et al. 1988). There is some support for the hypothesis that mossy fiber sprouting after kindling may facilitate DG throughput (Golarai and Sutula 1996; Houser et al. 1990; Isokawa et al. 1993; Sutula et al. 1989). For example, after kainate-induced mossy fiber sprouting, glutamate microstimulation in the granule cell layer evoked EPSPs in neighboring granule cells (Wuarin and Dudek 1996). Mossy fibers therefore may synapse on granule cells, resulting in feedback excitation. Okazaki et al. (1995) showed that mossy fibers develop recurrent collaterals after pilocarpine-induced status epilepticus. These collaterals formed synapses in the dentate molecular layer, but the authors did not provide an estimate for the proportion of recurrent mossy fiber boutons innervating granule cells versus other neurons. An inhibitory rather than an excitatory function of the reorganized dentate mossy fibers also has been proposed (Ribak and Peterson 1991; Sloviter 1992). Alternatively, sprouting, albeit common, may not be a prerequisite of epilepsy. A recent report (Longo and Mello 1997) demonstrated that cycloheximide blocked pilocarpine- and kainate-induced mossy fiber sprouting without preventing the development of spontaneous epileptic seizures.

In summary, kindling induces alterations in both the DG and area CA3 that lead to a facilitated spread of epileptiform activity through the HC. As EC seizures transmitted to the HC are first relayed by the DG, this structure plays a crucial role in epileptogenesis. Understanding how the DG loses its filter function in chronic temporal lobe epilepsy may provide critical insight into developing future antiepileptic medications aimed at preventing the spread of seizures in the HC-EC complex.

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