# Changes in Single L-Type Calcium Channel Currents in CA1 Pyramidal Neurons of Rat Hippocampus After Transient Forebrain Ischemia*

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**Abstract** It has been shown that intracellular $Ca^{2+}$ in hippocampal CA1 neurons is elevated during ischemia and at early period following reperfusion. This $Ca^{2+}$ overload has been suggested to be involved in ischemic brain damage. In normal CA1 neurons, the major mechanism allowing $Ca^{2+}$ entry from the extracellular compartment is the opening of voltage-gated $Ca^{2+}$ channels. The aim of the present study was to explore whether L-type calcium channel in hippocampal CA1 neurons changed at early period of reperfusion after ischemia. Transient forebrain ischemia in a duration of 15 min was induced by the use of the 4-vessel occlusion method in rats. Single L-type calcium currents were recorded in cell-attached patches of actually dissociated hippocampal CA1 neurons. After ischemia, average total patch current of L-type $Ca^{2+}$ channels significantly increased in CA1 neurons when compared with that of control. This ischemia-induced enhancement in channel function was due to a higher channel open probability. Further analysis of single channel kinetics showed a prolonged open time and an increased opening frequency in postischemic channels. It is suggested that the functional enhancement in L-type calcium channels may partially account for the postischemic increase in intracellular $Ca^{2+}$ concentration of CA1 neurons following ischemia.

**Key words** L-type calcium channels, ischemia, patch clamp, hippocampus, rat

Neurons in the central nervous system are highly sensitive to cerebral ischemia. Specially, the CA1 pyramidal neurons in the hippocampus are particularly vulnerable to ischemic insult[1, 2]. $Ca^{2+}$ overload has been suggested to be involved in this selective neuronal damage[3, 4] although the underlying mechanisms are not fully understood. This hypothesis has received its best support from many $Ca^{2+}$ imaging and pharmacological studies. For example, $Ca^{2+}$ influx[5] and cytoplasmic $Ca^{2+}$ in hippocampal CA1 neurons are increased during transient ischemia and can be toxic to neurons at early period after reperfusion[6, 7]. A variety of drugs that will be expected to limit neuronal damage in hippocampus from a $Ca^{2+}$ overload are neuroprotective when present during ischemia and also during early period of reperfusion[3, 4]. However, the influx pathways mediating the raised intracellular $Ca^{2+}$ after ischemia are still unclear. Most previous studies on the role of excessive $Ca^{2+}$ influx in cell death have focused on $Ca^{2+}$ entry via ligand-gated channels such as NMDA and AMPA receptors[8]. It is becoming increasingly recognized that voltage-gated calcium channels (VGCCs), particularly the L-type, can be a route for toxic levels of $Ca^{2+}$ influx after a number of insults[9, 10]. Furthermore, VGCCs represent a major $Ca^{2+}$ entry pathway even during the activation of ligand-gated $Ca^{2+}$ channels[11~13]. It is also becoming clear that $Ca^{2+}$ influx via different routes (voltage vs ligand-gated channel influx) may not be functionally interchangeable[14, 15]. In addition, L-type $Ca^{2+}$ channels are prevalent in hippocampal pyramidal neurons, contributing 30% ~ 50% of total calcium current[16]. So, we speculate L-type calcium channels likely play a crucial role in hippocampal CA1 pyramidal neuronal survival and death after transient forebrain ischemia in rat. The aim of our present study was to examine whether L-type calcium channel currents in CA1 pyramidal neurons of rat hippocampus were changed after transient forebrain ischemia using cell-attached configuration of patch clamp techniques.

## 1 Materials and methods

### 1.1 Animal model

Male adult Wistar rats weighing 200~220 g were subjected to transient forebrain ischemia (15 min) by use of the 4-vessel occlusion method[17~19] with some modification. Briefly, rats were anesthetized with chloral hydrate (ip, 35 mg/100 g), and both

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common carotid arteries were exposed for subsequent occlusion of these vessels. Both vertebral arteries were electrocauterized permanently. On the next day, the fully awake rats were restrained and the carotid clasps were tightened to produce 4-vessel occlusion. Severe transient forebrain ischemia was induced by occluding both common carotid arteries for 15 min. Upon release of the carotid artery clasps, cerebral blood flow resumed immediately. Signs such as unresponsiveness, loss of righting reflex, and catatonic postures, were thought to be indicative of forebrain ischemia. Rats with postischemic convulsions were excluded from study.

### 1.2 Acute-dissociation procedures

Pyramidal cells in hippocampal CA1 region were dissociated acutely from rats before ischemia and at 30 min following reperfusion using procedures as described previously[18,19]. Briefly, Wistar rats were anesthetized with chloral hydrate (ip, 35 mg/100 g) and then decapitated. Brains were quickly removed, iced, and blocked for slicing. The blocked tissue was cut into 400 μm thick slices with a Vibroslice whilst bathed in a low $Ca^{2+}$, HEPES-buffered salt solution containing 140 mmol/L sodium isethionate, 2 mmol/L KCl, 4 mmol/L $MgCl_2$, 0.1 mmol/L $CaCl_2$, 23 mmol/L glucose, 15 mmol/L HEPES, pH 7.4 (300 ~ 305 mOsmol/L). Slices were then incubated for 1 ~ 6 h at room temperature (20 ~ 22℃) in a $NaHCO_3$-buffered saline bubbled with 95% $O_2$-5% $CO_2$ containing 126 mmol/L NaCl, 2.5 mmol/L KCl, 2 mmol/L $CaCl_2$, 2 mmol/L $MgCl_2$, 26 mmol/L $NaHCO_3$, 1.25 mmol/L $NaH_2PO_4$, 10 mmol/L glucose, pH 7.4 with NaOH (300 ~ 305 mOsm/L). Slices were then removed into the low $Ca^{2+}$ buffer, and CA1 region of hippocampus was dissected out under a dissecting microscope and placed into an oxygenated chamber containing pronase (Sigma protease Type XIV, 1 ~ 1.5 g/L) in HEPES-buffered HBSS (Sigma) at 33℃. After 30 ~ 45 min of enzyme digestion, tissue was rinsed three times in the low $Ca^{2+}$, HEPES-buffered saline and dissociated mechanically with a graded series of fire-polished Pasteur pipettes. The cell suspension was then plated into a 35 mm Lux petri dish mounted on the stage of a microscope (Leica DMLFS) containing HEPES-buffered HBSS saline. After allowing the cell to settle, the solution bathing the cells was changed to our recording solution.

### 1.3 Single-channel current recording and data analysis

Cell-attached recording pipettes were pulled from glass capillary tubes using a micropipette puller (model P-97, Sutter Instruments, Novato, CA). The pipette resistance was 6 ~ 9 MΩ and the seal resistance was in excess of 5 GΩ. Recordings were obtained according to standard patch-clamp methods using an Axopatch 200B amplifier (Axon Instruments, CA), with the current filtered at 1 kHz and sampled at 5 kHz. Voltage pulses were delivered at 5 s intervals. Linear leak and capacitive currents were subtracted digitally. Electrophysiological recordings were performed at room temperature (22 ~ 24℃). Voltage commands were generated, and current responses were recorded and analyzed using a computerized acquisition and storage system (pCLAMP, version 8.0, Axon Instruments, CA).

To determine distributions for channel amplitudes and open times, a 50% threshold criterion was used to determine the durations of open events. Single channel conductance was estimated as the slope of the current-voltage relationship for L-type $Ca^{2+}$ channels recorded with 110 mmol/L $Ba^{2+}$ as the charge carrier. Current-voltage curves were generated using the current amplitude determined from Gaussian fits to amplitude histograms from individual patches. The ignored level for detecting events was limited to 300 μs. Logarithmic distributions of open durations were exponentially fitted with the use of the Least-Square algorithm method. Ensemble average (pseudomacroscopic) current responses were obtained for each patch from a series of 15 depolarizing pulses (300 ms duration) evoked from $V_h$ = 50 mV to $V_T$ = − 10 mV. Average total patch current ($I$) was determined by integrating the leak-subtracted ensemble average current trace from the zero baseline to the inward current envelope during the pulse and dividing the integral by the duration of the pulse (300 ms). Overall open probability ($P_o$) in response to a particular stimulus was calculated by evaluating all applicable sweeps during the entire recording including null sweeps. The total open time during the analyzed portion of the sweep was divided by the analysis time period. Only these cases included one level and clearly resolvable L-type openings were analyzed in open probability, open frequency and open time. But for patches that contained more than two of the same kind of channel were included in calculating average total current.

The data in text was expressed as ($\bar{x} \pm s$) and ANOVA (SPSS) was used for statistical analysis. Statistical significance was at $P < 0.05$.

### 1.4 Recording solutions and reagents

For cell-attached single-channel patch recording the extracellular bath solution contained 140 mmol/L potassium gluconate, 3 mmol/L $MgCl_2$, 10 mmol/L EGTA, 10 mmol/L glucose, 10 mmol/L HEPES, and 0.001 mmol/L TTX, pH 7.4 with KOH. This solution zeroes the membrane potential. The recording pipette

solution contained 110 mmol/L $BaCl_2$, 10 mmol/L TEA-Cl, and 10 mmol/L HEPES, pH 7.3 with TEA-OH. Bay K-8644 (500 nmol/L), a potent L-type $Ca^{2+}$ channel agonist, was added to the pipette to enhance recording of L-type channels. The osmolarity of all recording solutions was adjusted to 320~325 mOsmol/L as necessary, by the addition of sucrose. All chemicals were obtained from Sigma. Stock solutions of Bay K-8644 (RBI, Natick, MA) and nimodipine (RBI) were prepared in 100% ethanol, aliquoted, and frozen at −20℃ until subsequent use. The final concentration of ethanol in experimental drug solutions was 0.1%.

## 2 Results

### 2.1 Comparison of average total patch current before and after ischemia

The characteristics of L-type $Ca^{2+}$ channel in cell-attached patches from both control and ischemic neurons were consistent with those of reported previously[20,21]: high activation threshold, no obvious inactivation, high selectivity to $Ca^{2+}$, unitary conductance about 27 pS, and high sensitivity to L-type $Ca^{2+}$ channel agonist Bay K-8644 and antagonist nimodipine. Figure 1 showed representative original current traces of single L-type $Ca^{2+}$ channel and average total patch current from patches of CA1 neurons before and after ischemia. Average total patch current ($I$) in patches (evoked from $V_h$ = 50 mV to $V_c$ = −10 mV) was (0.439 ±0.058) pA in control ($n$= 25) and (1.517 ±0.312) pA in postischemic cells ($n$= 19), representing an approximate 4-fold increase at 30 min after reperfusion compared with control ($P$< 0.05).

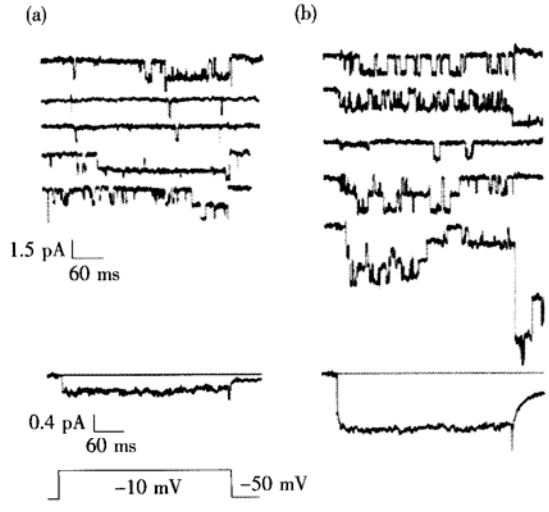


**Fig. 1 Five representative leak-subtracted recordings from a cell-attached patch on a CA1 neuron**

(a) shows recordings from control neuron. (b) shows recordings from postischemic neuron during repetitive depolarizations (−50 mV to −10 mV). All perfectly recorded patches were used to create an average total current for each neuron (shown below the five single traces). Voltage protocol is shown at the bottom.

### 2.2 Comparison of channel unitary conductance before and after ischemia

At fixed membrane potential, total patch current is determined by the single channel unitary conductance and the open probability ($P_o$). To determine which factors might be responsible for the overall change in total patch current, we firstly compared unitary conductance before and after ischemia. Single-channel amplitude ($i$) was measured at multiple test voltages in patches with clearly resolvable openings and the unitary conductance was determined by fitting a regression line through the data. As illustrated in Figure 2, the mean slope conductance of L-type calcium channels in postischemic neurons remained unchanged as compared with that of control neurons ($n$= 10, $P$> 0.05).

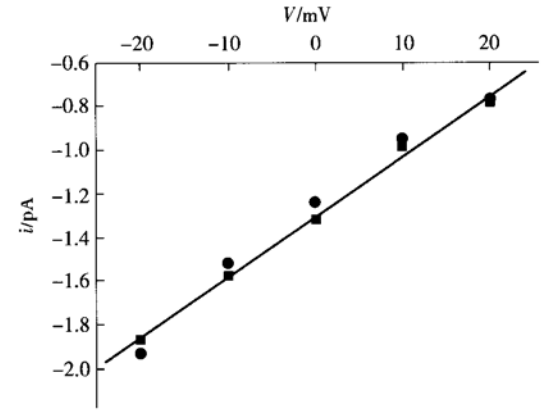


**Fig. 2 ($\bar{x} \pm s$) values for single-channel current amplitudes ($i$) during depolarization pulses to multiple test voltages in patches from animals before and 30 min after ischemia**

Individual values of $i$ represent the mean amplitude of all clearly resolvable L-type opening during the pulse for each patch at each voltage ($n$= 10 patches per group at each voltage). Mean slope conductance for each group was calculated from the average of individual patch slope conductance. No significant differences were seen in average single-channel current amplitude at any voltage or in slope conductance before and after ischemia. ■——■: control; ●——●: ischemia.

### 2.3 Comparison of channel open probability before and after ischemia

Figure 3 showed the voltage dependence of L-type calcium channel activity before and after ischemia. Individual $P_o$-$V$ curves were fitted by the Boltzmann equation $P_o = P_{max}[1+\exp((V_{1/2}-V)/K)]$, where $K$ is the membrane depolarization for an e-fold increase in $P_o$, and $V_{1/2}$ is the patch potential at which $P_o$ is one-half of the maximum $P_o$ ($P_{max}$). $V_{1/2}$ and $K$ could be obtained by plotting $P_o/P_{max}$ against membrane

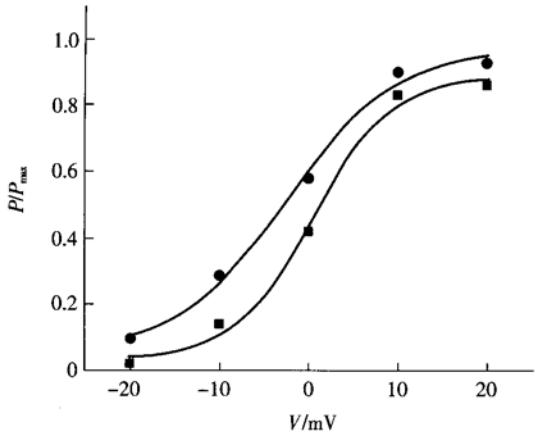


**Fig. 3 Comparison of voltage-dependent activation of L-type calcium channels in control and postischemic CA1 neurons**

Voltage dependence of activation represented by $P/P_{max}$ plotted against membrane potential. Smooth curves derived from the Boltzmann relation are given by $P/P_{max} = 1/\{1+\exp[(V_{1/2}-V)/K]\}$.

■—■: control; ●—●: ischemia

potential. The values of $V_{1/2}$ and $K$ were (6.61 ± 1.36) mV and (6.73 ± 1.24) mV for control ($n$ = 10), (−2.36 ± 0.69) mV and (7.31 ± 0.86) mV for ischemia ($n$ = 10), respectively. Statistical analysis showed that there was not significant difference in the $K$ value between two groups ($P > 0.05$) while the value of $V_{1/2}$ was significantly decreased after ischemia when compared with control ($P < 0.01$), indicating an increase in the open probability but without alteration of voltage dependence in postischemic channels.

### 2.4 Comparison of channel kinetics before and after ischemia

At a given holding voltage, the open probability is determined by channel open time and open frequency. To understand which one is the major component contributing to the differences in open probability before and after ischemia, kinetics of single L-type calcium channels were compared between two groups. Figure 4 showed open time histograms constructed from membrane patches depolarized to − 10 mV.

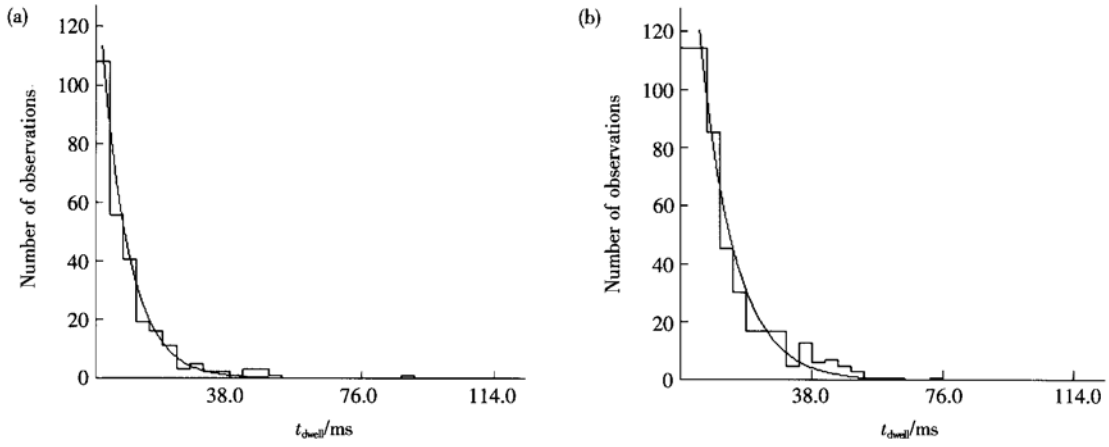


**Fig. 4 Distributions for open time of L-type calcium channels in control (a) and postischemic neurons (b)**

All histograms of dwell time could be well-fitted by a one-exponential function. $V_H$ = − 50 mV, $V_T$ = − 10 mV.

The distributions of open time of L-type calcium channels from both groups could be fitted well by single-exponential function. Significant change was observed in the open time constants of the L-type calcium channel after ischemia. Open time constants were (6.17 ± 0.26) ms for control, (9.42 ± 0.28) ms for ischemia ($n$ = 10, $P < 0.05$, $V_H$ = − 50 mV, $V_T$ = − 10 mV). The open frequency was also changed at 30 min of reperfusion as compared with control ($P < 0.05$) (Figure 5).

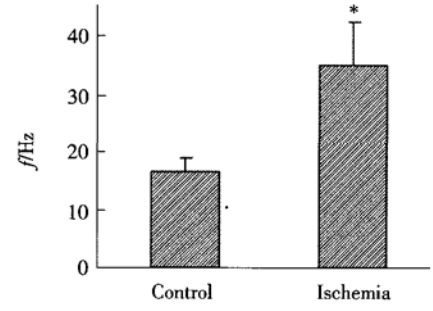


**Fig. 5 Comparison of open frequency of L-type calcium channels in control and post-ischemic CA1 neurons**

Open frequency was increased at 30 min of reperfusion as compared with control. * $P < 0.05$.

## 3 Discussion

We report the first recordings of single L-type calcium channel currents in CA1 pyramidal neurons of adult rat hippocampus prepared 30 min after *in vivo* ischemia. The principal finding of the present study is that L-type calcium currents of rat hippocampal CA1 neurons are enhanced, due to an increase in channel open probability, at early period of reperfusion after transient forebrain ischemia. The results may partially account for the postischemic changes in intracellular $Ca^{2+}$ of CA1 neurons following ischemia[5~7], and support the $Ca^{2+}$ overload hypothesis, at least in part, from electrophysiological aspect. It has been shown that, in addition to glutamate receptor antagonists, the L-type $Ca^{2+}$ channel antagonists nifedipine and verapamil can also inhibit the ischemic $Ca^{2+}$ accumulation and protect the ischemic neuronal damage in the CA1 region of rat hippocampus[3,4,22]. Taken together, it appears that the increase in L-type $Ca^{2+}$ current at the early phase of reperfusion may be one of the influx pathways leading to acute postischemic $Ca^{2+}$ overload during this period.

Our single channel analysis showing an increased open probability without alteration of unitary conductance suggest that one possible mechanism underlying the enhancement of L-type $Ca^{2+}$ channel currents is the changes in the number and/or the properties of functionally available L-type $Ca^{2+}$ channels in postischemic CA1 neurons. There may be two possibilities. Firstly, ischemia may induce the formation of new channels in CA1 neurons. Actually, it has been shown that the mRNA and protein levels of L-type $Ca^{2+}$ channel is elevated during aging in cultured hippocampal neurons[21], implying that the expression of this kind of channel could be also modulated by ischemia. However, considering the fact that protein synthesis in vulnerable neurons was inhibited after ischemia, especially during early reperfusion[4], it is unlikely that the enhancement of L-type $Ca^{2+}$ channel at the early phase of reperfusion is due to an increased production of new L-type $Ca^{2+}$ channels. Secondly, ischemia may lead to activate the previously silent channels or modulate the previously functional channels. That is to say, the channel availability and properties including open time, open frequency and so on may be altered after ischemia. It has been shown that the availability and properties of L-type calcium channel can be modulated by oxidant and reductor via oxidation and reduction or protein kinases and phosphatses through phosphorylation and dephosphorylation[23,24]. Indeed, ischemia induces an accumulation of reactive free radical species in hippocampal CA1 neurons[4] and this increase in the oxidative potential has been suggested as an important modulator of BK channels in postischemic CA1 neurons[25]. Moreover, changes in activity or translocation of protein kinases and phosphatases are observed in hippocampal CA1 neurons after ischemia[4,26]. Therefore, it is reasonable to assume that the ischemia-induced changes in L-type calcium channels may be mediated by phosphorylation/dephosphorylation or redox modulation of the channels. Further experiments are needed to clarify these issues.

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# 大鼠全脑缺血后海马 CA1区锥体神经元 L型钙通道电流的改变*

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**摘要** 已有研究表明在脑缺血期间及再灌流后早期, 海马 CA1锥体神经元细胞内钙浓度明显升高, 这一钙超载被认为是缺血性脑损伤的重要机制之一. 电压依赖性钙通道是介导正常 CA1神经元钙内流的主要途径. 实验观察了脑缺血再灌流后早期海马 CA1锥体神经元电压依赖性 L型钙通道的变化. 以改良的四血管闭塞法制作大鼠 15 min前脑缺血模型, 在急性分离的海马 CA1神经元上, 采用膜片钳细胞贴附式记录 L型电压依赖性钙通道电流. 脑缺血后 CA1神经元 L型钙通道的总体平均电流明显增大, 这是由于通道的开放概率增加所致. 进一步分析单通道动力学显示, 脑缺血后通道的开放时间变长, 通道的开放频率增大. 研究结果提示 L型钙通道功能活动增强可能参与了缺血后海马 CA1锥体神经元的细胞内钙浓度升高.

**关键词** L-型钙通道, 缺血, 膜片钳, 海马, 大鼠
**学科分类号** R743. 31

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