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Properties of Large Conductance Calcium-Activated Potassium Channels in Pyramidal Neurons from the Hippocampal CA1 Region of Adult Rats

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Abstract: The properties of large-conductance Ca^{2+}-activated K^+ (BK_{Ca}) channels were studied in rat hippocampal CA1 pyramidal neurons by using the patch-clamp technique in the excised-inside-out-patch configuration. The lowest $[Ca^{2+}]_i$ in which BK_{Ca} channel activities were observed was 0.01 μM with the membrane potential of +20 mV and the $[Ca^{2+}]_i$ at which P_o of the channel is equal to 0.5 was 2 μM. The unitary conductance of the single BK_{Ca} channel was 245.4 pS with symmetrical 140 mM K^+ on both sides of the excised membrane. With a fixed $[Ca^{2+}]_i$ of 2 μM, P_o increased *e*-fold with a 17.0 mV positive change in the membrane potential. Two exponentials, with time constants of 2.8 ms and 19.2 ms at the membrane potential of +20 mV with 2 μM $[Ca^{2+}]_i$, were required to describe the observed open time distribution of BK_{Ca} channel, suggesting the existence of two distinct open channel states with apparently normal conductance. A BK_{Ca} channel occasionally entered an apparent third open channel state with the single channel current amplitude about 45% of the normal amplitude. The properties of BK_{Ca} channel, which were found in this study to be more steeply dependent on voltage and more sensitive to $[Ca^{2+}]_i$ in adult hippocampal neurons than in cultured or immature hippocampal neurons, may be responsible for the shortened duration of action potential in hippocampal CA1 pyramidal neurons of adult rat. [Japanese Journal of Physiology 51, 725–731, 2001]

Key words: BK_{Ca} channel, pyramidal neuron, patch clamp, hippocampus, rat.

Ca^{2+}-activated K^+ currents/channels have been described in a great many nonneuronal cells [1–4] and in neurons [5–13]. Single-channel studies have identified at least two types of channels (BK_{Ca} and SK_{Ca}, large conductance and small conductance Ca^{2+}-activated K^+ channels) in neuronal membranes on the basis of their pharmacological and biophysical properties [14, 15]. In neurons *in vivo*, BK_{Ca} channel is thought to be activated by Ca^{2+} ions entering the cell during the rising phase of the action potential and seems to be mainly responsible for the last two thirds of the spike repolarization and the fast after-hyperpolarization (fAHP) [16–18]. Evidence supporting this hypothesis is the findings that the spike broadens and the fAHP disappears when BK_{Ca} channels are blocked by external administration of TEA (0.5–1 mM) or Ca^{2+}-channel blockers, or by an intracellular injection of a fast Ca^{2+} chelator, BAPTA [14, 19–21].

In recent years, many data concerning BK_{Ca} channel have been obtained by the use of patch clamp techniques in cultured or immature neurons [5–7, 9–14]. In contrast, most studies concerning the BK_{Ca} channel's role in spike repolarization, and fAHP [16, 21, 22] have used recordings from slices of adult brain or *in vivo* recordings. Little is known so far about the properties of the BK_{Ca} channel in adult neurons. It is therefore desirable for the single channel properties of BK_{Ca} channel to be studied also in adult neurons.

The experiments in this study were designed primarily to extend the observations on the properties of the individual BK_{Ca} channel in CA1 pyramidal neurons from adult rat hippocampus.

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MATERIALS AND METHODS

Acute-dissociation procedures. Pyramidal cells in the hippocampal CA1 region from male adult rats (weighing 200–250 g) were acutely dissociated, using procedures described previously [23–25] with some modifications. In brief, rats were anesthetized with chloral hydrate (I.P., 40 mg/100 g body weight), then decapitated; brains were quickly removed, iced, and blocked for slicing. The blocked tissue was cut into 400 μm slices with a Vibroslice while being bathed in a low Ca^{2+} (100 μM), HEPES-buffered salt solution containing (in mM) 140 sodium isethionate, 2 KCl, 4 $MgCl_2$, 0.1 $CaCl_2$, 23 glucose, and 15 HEPES, pH 7.4 (300–305 mOsm/*l*). Slices were then incubated for 1–6 h at room temperature (20–22°C) in an $NaHCO_3$-buffered saline bubbled with 95% O_2/5% CO_2 containing (in mM) 126 NaCl, 2.5 KCl, 2 $CaCl_2$, 2 $MgCl_2$, 26 $NaHCO_3$, 1.25 NaH_2PO_4, 1 pyruvic acid, 0.005 glutathione, 0.1 N^{ω}-nitro-L-arginine, 1 kynurenic acid, and 10 glucose, pH 7.4 with NaOH (300–305 mOsm/*l*). All reagents were obtained from Sigma (St. Louis, MO). Slices were then transferred into the low Ca^{2+} buffer, and the CA1 region of hipocampus was dissected out under a dissecting microscope and transferred to an oxygenated chamber containing pronase (Sigma protease Type XIV, 1–3 mg/ml) in HEPES-buffered HBSS (Sigma) at 33°C. After 30–45 min of enzyme digestion, the 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 transferred to a 35 mm Lux petri dish mounted on the stage of an inverted microscope containing HEPES-buffered HBSS saline. After allowing the cells to settle, the bathing solution was changed to the recording solution. All reagents were purchased from Sigma.

Single-channel current recording. Gigaseal patch recordings using the inside-out patch configuration as described by Hamill *et al.* [26] (the feedback resistor was 50 GΩ) were performed on neurons with pyramidal shapes at room temperature. The pipette resistance was 8–12 MΩ, and the seal resistance exceeded 3 GΩ. Single-channel currents were recorded in excised inside-out patches, which were prepared by having the patch electrode pulled away from the pyramidal cells. The composition of the flow solution that bathed the intracellular face of the patch membrane after excision was (in mM) 140 KCl, 10 NaCl, and 10 HEPES. For solutions with a desired free calcium of less than 5 μM, 500 μM EGTA (ethyleneglycol-bis-(β-amino-ethylether)N,N′-tetraacetic acid) and $CaCl_2$ were added to the solution to obtain the desired level of total free calcium [27]. The desired free Ca^{2+} concentrations and the nominal Ca^{2+} concentration in the solution with 500 μM EGTA were 0.01 μM free Ca^{2+} and 55.7 μM Ca^{2+}; 0.1 μM free Ca^{2+} and 279 μM Ca^{2+}; 0.5 μM free Ca^{2+} and 435 μM Ca^{2+}; and 2 μM free Ca^{2+} and 485 μM Ca^{2+}. For a solution with a desired free Ca^{2+} of 5 μM or higher, EGTA was omitted and $CaCl_2$ was added as required. Solutions were adjusted to a final pH of 7.40. The pipette solution consisted of either the bathing solutions to give symmetrical charge-carrier distribution or a low concentration of K^+ solution (5 mM K^+). $MgCl_2$ at 0.5 mM was routinely added to the pipette solution purely for easier seal formation in the absence of other divalent ions.

The single-channel currents were recorded by use of a CEZ-2300 patch clamp amplifier (Nihon Kohden, Tokyo), with the current filtered (−3 dB, four-pole Bessel filter) at 1 kHz. Data were digitized at sampling rates of 10 kHz by use of a TL-125 kHz interface (Scientific Solutions). The analysis routines used a pClamp (version 5.5.1, Axon Instruments) to determine distributions for channel amplitudes and open and closed times. An automated 50% threshold crossing routine was used to detect channel transition, and all data were obtained at room temperature (20–22°C). The data in the text were expressed as mean±SD.

RESULTS

The channel recorded was highly selective for K^+, because its current–voltage relation reversed at 3.2±2.3 mV (n=18), very close to the equilibrium potential for potassium ion (E_K), with symmetrical K^+ (140/140 mmol/*l*) and the reversal potential shifted in a negative direction to −59.8±9.2 mV (n=18) with a low concentration of K^+ (5 mM) in the pipette. A similar observation was also reported in neocortical pyramidal neurons [12]. The activities of the channel recorded were affected by Ca^{2+} concentrations at the intracellular membrane surface, $[Ca^{2+}]_i$, of excised membrane patches. Whereas submicromolar concentrations of Ca^{2+} at the inner membrane surface were sufficient to activate the BK_{Ca} channel, 100 μM Ca^{2+} at the extracellular membrane surface activated no channels at any membrane potentials tested in this study (from −50 mV to +50 mV). Current–voltage relations indicated that the channel had high unitary conductance of approximately 245 pS. These three points served as keys to identification of the channel recorded as the BK_{Ca} channel.

Besides the BK_{Ca} channel, the membrane patches typically contained other channels with smaller conductance (or smaller conductances) than that of the

BK_{Ca} channel. These additional channels with smaller conductance will not be considered in this paper, and we have typically selected records in which they are not obviously present.

We also found an inactivation of BK_{Ca} channels as described by Hicks *et al.* [28]. To remove the inactivation of BK_{Ca} channels recorded at depolarization, all recordings at membrane depolarization were preceded by a hyperpolarization step of −60 mV for at least 1 min.

To determine the unitary conductance of BK_{Ca} channel, we measured amplitudes of the single channel current at various membrane potentials, and the unitary conductance of BK_{Ca} channel was determined by fitting a regression line through the data points. Examples of these currents evoked at varying membrane potentials were shown in Fig. 1A from an inside-out configuration of an adult pyramidal neuron in CA1 region with 0.1 μM $[Ca^{2+}]_i$. The greater the amplitude of the membrane potential, the greater the amplitude of the outward current. With symmetrical K^+ (140/140 mM) in both the pipette and the bath solutions, the reversal potential was close to 0 mV. The current–voltage relationship was plotted in Fig. 1B. The current–voltage relationships were fitted with a straight line having a slope conductance of 245.4±19.1 pS (Fig. 1B). The channel showed no rectification at all membrane potentials tested.

An individual P_o–V curve was fitted with the Boltzmann equation $P_o=P_{o,max}/\{P_{o,max}+\exp[(1/K)(V_{1/2}-V)]\}$ with 2 μM $[Ca^{2+}]_I$, and the voltage dependence of the BK_{Ca} channel was determined. The equation was transformed into the logarithmic form, $V=V_{1/2}+K\times\ln\{P_o/[P_{o,max}(1-P_o)]\}$, 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 half the maximum P_o ($P_{o,max}$). $V_{1/2}$ and K could be obtained by plotting $\ln\{P_o/[P_{o,max}(1-P_o)]\}$ against voltage (Fig. 2). The values of $V_{1/2}$ and K were 2.6 and 17.0 mV, respectively, indicating that P_o of BK_{Ca} channel increases e-fold for each 17.0±0.7 mV (n=10) positive change in membrane potential.

To further demonstrate the sensitivity of the BK_{Ca} channel to $[Ca^{2+}]_i$, recordings were obtained with different Ca^{2+} concentrations at the cytosolic face of the excised membrane. Figure 3 plotted the relationship between P_o and $[Ca^{2+}]_i$. In constructing this plot data with each $[Ca^{2+}]_i$ we averaged the data from 20 different membrane patches. At a membrane potential of +20 mV, the open probability of a BK_{Ca} channel increased to 83.3%, from 0.0056%, as $[Ca^{2+}]_i$ increased to 100 μM, from 0.01 μM. It was shown in Fig. 3 that there was a steep relationship between open probability vs. $[Ca^{2+}]_i$ over a range of 0.5 to 5 μM and that the

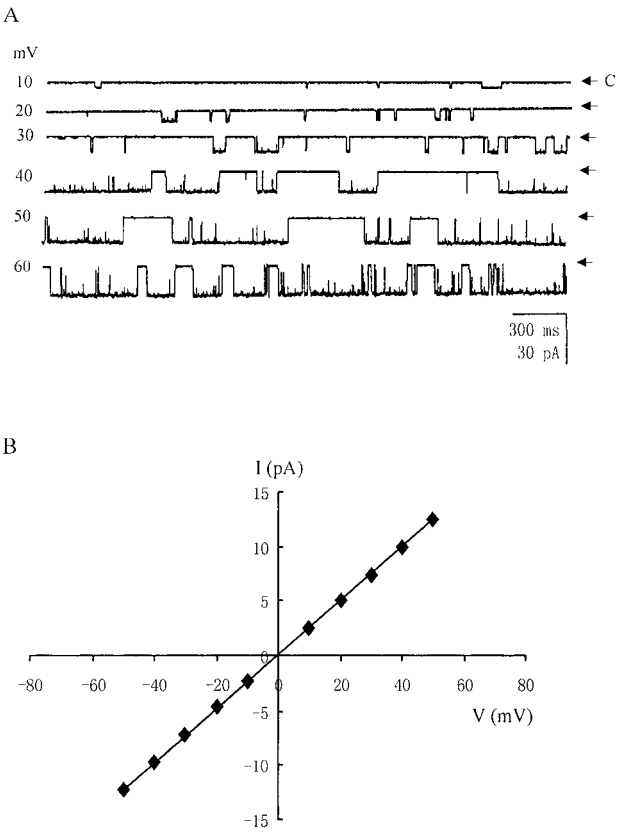

Fig. 1. Voltage dependence of the BK_{Ca} channel activity in an excised, inside-out patch of somatic membrane from hippocampal CA1 pyramidal neurons of adult rat. **A**: Segments of single-channel records showing K^+ currents through a single BK_{Ca} channel at varying membrane potentials in symmetrical 140 mM K^+ solutions (excised, inside-out configuration) with 2 μM $[Ca^{2+}]_i$. From the top trace to the bottom, the membrane potential was +10, +20, +30, +40, +50, and +60 mV, respectively. The outward currents evoked are shown as downward deflections. **B**: Plots of single channel current amplitudes (I) against membrane potentials (V). The line fitted to the data points gave a slope conductance of approximately 245 pS.

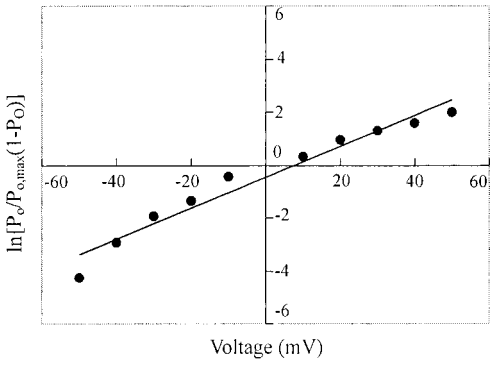

Fig. 2. Quantitative analysis of voltage dependence of BK_{Ca} channel. Logarithmic Boltzmann fittings of P_o–V curve for representative single BK_{Ca} channel from CA1 pyramidal neurons.

slope of the relationship for lower or higher levels of $[Ca^{2+}]_i$ was reduced. The $[Ca^{2+}]_i$ at which the channel was half activated was 2 μM. Whereas $[Ca^{2+}]_i$ had pronounced effects on channel activity, it had little effect on single channel current amplitudes, which remained relatively constant for $[Ca^{2+}]_i$ ranging from 0.1 to 100 μM. Furthermore, single channel current amplitudes appeared to remain constant to 0.01 μM $[Ca^{2+}]_i$ if the limited frequency response of the patch clamp was taken into account by measuring only those currents where the channels were open sufficiently long enough for the recording system to record the peak current.

A detailed kinetic analysis was usually precluded by the presence of multiple active channels in the patch. Figure 4 showed detailed kinetic data from a patch in which only a single channel was observed with 2 μM $[Ca^{2+}]_i$ with membrane potential of +20 mV. In general, the open time distribution was fitted satisfactorily with a double exponential function. This was shown in Fig. 4A, in which the open time histogram is plotted for 2 μM $[Ca^{2+}]_i$. The histogram was fitted with a double exponential with the time constant of 2.8±2.1 and 19.2±10.1 ms (n=15). The closed time distribution also required a double exponential for a reasonable fit (Fig. 4B) with the time constant of 2.7±1.6 and 26.9±17.9 ms (n=15).

Figure 5 presented records in which the channel appeared to enter a conductance state (indicated by dots) in which the current through a single channel was about 45% of normal. Reduced single channel currents of this type were observed in 13 of 147 experiments. Openings with reduced current amplitude typically comprised less than 0.3% of the total channel open time and had little effect on the result in the previous sections. It seemed impossible that this apparent reduced conductance state arose from a separate channel with 45% amplitude of BK_{Ca} channel, since such a

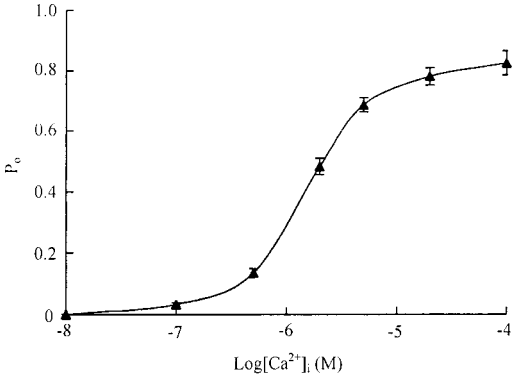

Fig. 3. Effects of $[Ca^{2+}]_i$ on BK_{Ca} channel activity in excised membrane patches. Plots of P_o of BK_{Ca} channel against log$[Ca^{2+}]_i$. One hundred percent indicates that BK_{Ca} channel was continuously open. Membrane potential, +20 mV; 100 μM $[Ca^{2+}]_o$. Note that P_o with each $[Ca^{2+}]_i$ was averaged from 20 different membrane patches.

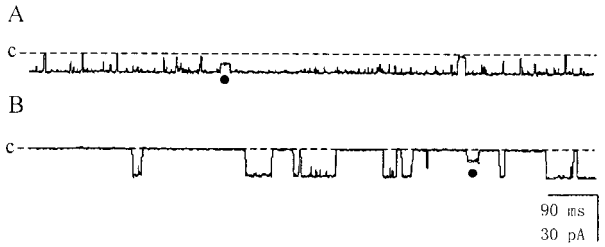

Fig. 5. Multiple conductance states of BK_{Ca} channel. Segments of records of membrane currents with normal and reduced (dots) single-channel current amplitudes. Reduced current amplitude was 40% of normal. Outward currents evoked were shown as downward deflections. **A**: A trace showing a reduced conductance state appeared to be entered directly from an open channel state of normal conductance without passing through an obvious closed channel state. Membrane potential, +40 mV; 5 μM $[Ca^{2+}]_i$. **B**: A trace showing a reduced conductance state recorded between apparently closed channel states. Membrane potential, +60 mV; 0.1 μM $[Ca^{2+}]_i$. The calibration in B also applied to A.

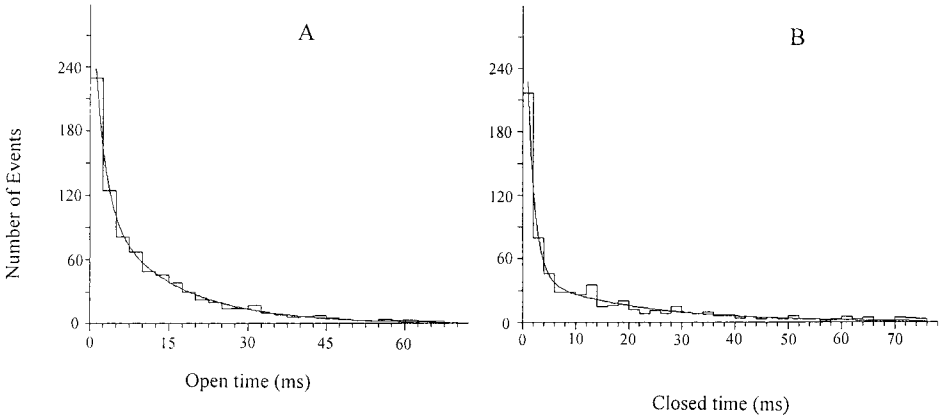

Fig. 4. Representative distributions of single BK_{Ca} channel characteristics. A: Open distribution of a single BK_{Ca} channel recorded at membrane potential of +20 mV in the presence of 2 μM $[Ca^{2+}]_i$. The distribution was fitted with a two-exponential function with a time constant of 2.1 ms and 14.4 ms. **B**: A closed distribution of a single BK_{Ca} channel in the same conditions as in A. The closed distribution was fitted with a two-exponential function with a time constant of 1.5 ms and 21.5 ms.

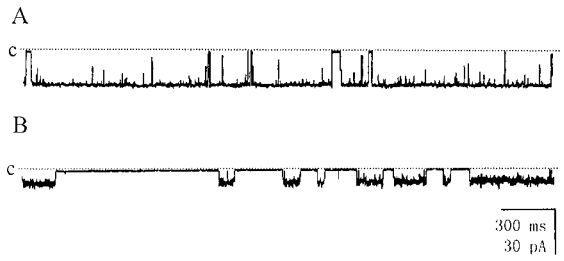

Fig. 6. Effects of external TEA on BK_{Ca} channel. Note that each trace was from different membrane patches. With 0.5 mM TEA in the pipette solution, BK_{Ca} channel's apparent unit current amplitude was reduced (**B**) compared with normal (**A**) by rapid blocking events that could not be resolved. Outward currents evoked were shown as downward deflections. Membrane potentials, +80 mV; $[Ca^{2+}]_i$, 0.5 μM. The calibration in B also applied to A.

channel was not observed in isolation.

The BK_{Ca} channel was quite sensitive to a low concentration (0.5 mM) of external TEA, a K^+ channel blocker (TEA was included in the pipette solution, Fig. 6). The 2 recordings in Fig. 6 were from different patches, but the apparent conductance of the channel was reduced in the presence of TEA (Fig. 6B). The most likely explanation for the reduction in conductance by TEA was a rapid, unresolved block (note the increased noise during channel openings), which caused an apparent decrease in the unit current amplitude. The BK_{Ca} channel was not affected by the administration of TEA to the intracellular side of membrane at either membrane potential tested.

DISCUSSION

The properties of BK_{Ca} channel was examined in excised membrane patches of hippocampal CA1 pyramidal neurons from adult rat by use of an inside-out configuration of patch clamp techniques. We found that the open frequency of the channel and open probability increased with increasing $[Ca^{2+}]_i$ and/or depolarization. The observed open distribution of BK_{Ca} channel was described by the sum of two exponentials, and the channel occasionally entered a state with a single channel current 45% of the normally observed single BK_{Ca} channel current amplitude.

This paper also provided evidence that pyramidal neurons in hippocampal CA1 region from adult rats has a large conductance Ca^{2+}-activated K^+ channel that is activated by intracellular $[Ca^{2+}]_i$. Although the conductance of a BK_{Ca} channel in adult hippocampal CA1 pyramidal neurons (245 pS) was slightly higher than in cultured hippocampal neurons (220 pS), the BK_{Ca} channel in hippocampal neurons ([8–11], the present study) has properties similar to those that have been reported in other cell types, namely, large conductance (approximately 200 pS), voltage dependence, and sensitivities to $[Ca^{2+}]_i$ or external TEA [2–4, 6, 7, 19, 27].

The $[Ca^{2+}]_i$ concentration in the resting CA1 pyramidal neurons is estimated as 100 nM, and this increases to 500–600 nM after the action potential. In some pathological conditions, such as forebrain ischemia, it may reach as high as 1–2 μM [29, 30]. Our results showed a steep relationship between open probability between $[Ca^{2+}]_i$ over the range between 0.5 and 5 μM, and the slope of the relationship for lower or higher levels of $[Ca^{2+}]_i$ was reduced (Fig. 3). The activities of the BK_{Ca} channel were first observed at 0.01 μM of $[Ca^{2+}]_i$ and increased with $[Ca^{2+}]_i$. The $[Ca^{2+}]_i$ at which P_o of the channel is 0.5 was 2 μM. Previous data from cultured hippocampal neurons showed that the steep relationship between open probability vs. $[Ca^{2+}]_i$ was from about 1 to 10 μM; the activity was first observed at 1 μM $[Ca^{2+}]_i$; and the $[Ca^{2+}]_i$ at which P_o of the channel is 0.5 was 4 μM [8]. Studies on newborn hippocampal neurons observed that 14.5 4 μM are required to activate BK_{Ca} channels with P_o of 0.5 [10]. Meanwhile, the present study showed that P_o of BK_{Ca} channel increases *e*-fold for each 17.0 mV positive change in membrane potential, less than 22 mV in cultured hippocampal neurons [11]. Taken together, it is implied that the BK_{Ca} channel in adult hippocampal neurons is more dependent on voltage and more sensitive to $[Ca^{2+}]_i$ than in cultured or newborn hippocampal neurons.

The present study exhibited that two exponential functions were required to describe the open distribution of the BK_{Ca} channel (Fig. 4A) and that the BK_{Ca} channel occasionally entered an open state with a single channel current amplitude of 45% of the normally observed single channel current amplitude (Fig. 5), suggesting at least three open channel states of the BK_{Ca} channel in adult hippocampal CA1 pyramidal neurons, namely, two states of an apparently normal conductance with different mean open times and a third with a reduced conductance. All three states were observed in current records from a patch containing only a single channel, indicating that a single BK_{Ca} channel can enter all three open channel states. But only one open state was observed in cultured or neonatal hippocampal neurons [8–10].

In our records a reduced conductance state appeared to enter directly from an open channel state of normal conductance without passing through an obvious closed channel state; it then returned directly to the normal conducting state before closing fully (Fig. 5A). This observation suggested that the reduced con-

ductance state is in series with a normal conducting state. However, we did not exclude the possibility that the reduced conductance state was preceded and followed by a closed channel state too brief to be detected by our recording system. This phenomenon was also found in cultured muscle [3]. Labarca and Miller [31] had observed the existence of two conductance states observed in a K^+ channel from sarcoplasmic reticulum; in their preparation, however, the reduced conductance state was preceded and followed by the higher conductance state. The existence of several conducting states had been reported in an acetylcholine-activated channel [32]. It is found that the reduced conducting state is preceded, but not followed, by the higher conductance state. Meanwhile, a reduced conductance state was also recorded between apparently closed channel states in our results (Fig. 4B). The reduced conductance channel state was not observed in cultured or newborn hippocampal neurons [8–11].

BK_{Ca} channels play crucial roles in the regulating of fAHP and the duration of action potential [14, 18–21], and a previous study had demonstrated a decrease in the duration of action potential with age in hippocampal CA1 neurons [33]. Therefore, the properties of BK_{Ca} channels in adult rat reported in the present study, more dependence on voltage and more sensitivity to intracellular calcium than in neonatal rat, may contribute to the shortened duration in action potential of hippocampal CA1 neurons from adult rat.

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