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Roles of Ca^{2+}-Activated K^+ Conductances on Spontaneous Firing Patterns of Isolated Rat Medial Vestibular Nucleus Neurons

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To investigate the contributions of intrinsic membrane properties to the spontaneous activity of medial vestibular nucleus (MVN) neurons, we assessed the effects of blocking large and small calcium-activated potassium channels by means of patch clamp recordings. Almost all the MVN neurons recorded in neonatal (P13–P17) rat were shown to have either a single deep after-hyperpolarization (AHP; type A cells), or an early fast and a delayed slow AHP (type B cells). Among the recorded MVN cells, immature action potential shapes were found. Immature type A cell showed single uniform AHP and immature B cell showed a lack of the early fast AHP, and the delayed AHP was separated from the repolarization phase of the spike by a period of isopotentiality. Application of apamin and charybdotoxin (CTX), which selectively block the small and large calcium-activated potassium channels, respectively, resulted in significant changes in spontaneous firings. In both type A and type B cells, CTX (20 nM) resulted in a significant increase in spike frequency but did not induce bursting activity. By contrast, apamin (300 nM) selectively abolished the delayed slow AHP and induced bursting activity in type B cells. Apamin had no effect on the spike frequency of type A cells. These data suggest that there are differential roles of apamin and CTX sensitive potassium conductances in spontaneous firing patterns of MVN neurons, and these conductances are important in regulating the intrinsic rhythmicity and excitability.

Key Words: MVN neuron, Acute isolated neuron, Spontaneous activity, Calcium activated potassium channels, Bursting

INTRODUCTION

Spontaneous electrical activity is seen in a wide variety of neurons in the CNS (Llinas, 1988), including thalamic neurons (McCormick & Pape, 1990), neurons releasing monoamine transmitter such as dopamine, serotonin and histamine (Yung et al, 1991; Uteshev et al, 1995; Bayliss et al, 1997), and GABAergic interneurons of the hippocampus and cerebral cortex (Alger & Nicoll, 1980; Salin & Prince, 1996). Medial vestibular nucleus (MVN) neurons are found to have resting activity with frequency of 10 to 20 spikes/sec (Darlington et al, 1995). The steady spontaneous discharge of MVN cells is due to intrinsic pacemaker-type membrane ionic conductances which depolarize them to firing threshold. While the ionic mechanisms underlying spontaneous firing are incompletely understood, it is likely that the intrinsic excitability of MVN neurons will have important implications for the normal processing of vestibular information and may also be important in compensatory changes in the vestibular nuclear complex (Dutia et al, 1992; Darlington & Smith, 1996). Two types of tonically active MVN neurons have been described. Type A MVN neurons were characterized by a broad action potential and a large single afterhyperpolarization (AHP). Type B MVN neurons had a narrower action potential followed by an early fast AHP and a delayed slow AHP (Serafin et al, 1991; Johnston et al, 1994). A major difference between type A and type B MVN cells lies in the effects

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of the selective small conductance Ca^{2+}-activated K^+ channel (SK_{Ca}) blocker apamin, which has only a small effect on the AHP in type A cells while selectively abolishing the delayed slow AHP, but not the early fast AHP, in type B cells (Johnston et al, 1994).

Ca^{2+} activated K^+ currents have been reported to play important roles in the regulation of neuronal activity. In particular, these currents were shown to 1) contribute to the repolarizing phase of the action potential (Adams et al, 1982); 2) control the repetitive discharge of spikes (Constanti & Sim, 1987; Schwindt et al, 1988); and 3) participate in various forms of oscillatory membrane behavior (Bourque, 1988). Single channel studies have revealed several types of Ca^{2+}-activated K^+ channels, which can be divided into two distinct groups on the basis of their pharmacological and biophysical properties: large-conductance Ca^{2+}-activated K^+ channel (BK_{Ca}) and small-conductance Ca^{2+}-activated K^+ channel (SK_{Ca}) (Barrett et al, 1982; Blatz & Magleby, 1987). The BK_{Ca} channels have a high unitary conductance and display sensitivity to both voltage and submicromolar concentrations of charybdotoxin (CTX). The current passing through these channels has been implicated in action potential repolarization and the fast hyperpolarization after the spike (Adams et al, 1982). In contrast, SK_{Ca} channels have a low unitary conductance, are voltage- and CTX-insensitive, and are activated by nanomolar concentration of calcium. The current flowing through these channels is sensitive to apamin and was shown to underlie the slow AHP that in many cells is responsible for action potential frequency adaptation (Madison & Nicoll, 1984; Lancaster et al, 1991).

Our previous studies have described a number of different potassium currents, including delayed rectifier current, A-current, large conductance Ca^{2+}-activated K^+ current and small conductance Ca^{2+}-activated K^+ current in MVN neurons (Chun et al, 1999), but yet little is known about the role of Ca^{2+}-activated K^+ currents in these neurons. To assess the functional properties of these conductances further, we examined in the present study the effects of two Ca^{2+}-activated channel blockers on the spontaneous discharge patterns of MVN neurons.

METHODS

Cell preparation

MVN neurons were dissociated according to the methods of Kay & Wong (1986) and Akaike et al (1990) after minor modification. 13- to 17-day-old Sprague-Dawley rats of both sexes were anesthetized with ether and decapitated. The brainstem was rapidly dissected and submerged in 4°C artificial cerebrospinal fluid (ACSF). The slices of brainstem, cut coronally 400 μm in thickness, were made with a vibroslicer (DTK 1000, Dosaka, Japan). These slices were pre-incubated in an ACSF well saturated with 95% O_2 - 5% CO_2 at room temperature for 1 hr. Thereafter, the slices were treated with 0.2 mg/ml pronase for 30~60 min at 32°C and subsequently exposed to 0.2 mg/ml thermolysin under the same conditions. After enzyme treatment, the slices were kept in an enzyme-free ACSF. The portion of MVN neurons was removed by micropunching. MVN neurons were dissociated into single cells by pipetting with a Pasteur pipette that had a fire-polished tip to reduce damage to the cells. The dissociated neurons were transferred into a recording chamber (volume of chamber, 0.5 ml) mounted on an inverted microscope (CK-2, Olympus, Japan).

Solutions

The ionic composition of the ACSF was (in mM) 124 NaCl, 5 KCl, 1.2 KH_2PO_4, 1.3 $MgSO_4$, 2.4 $CaCl_2$, 10 glucose and 24 $NaHCO_3$ and was bubbled continuously by 95% O_2 - 5% CO_2. The patch pipettes were filled with a solution containing (in mM); 140 KCl, 1 $MgCl_2$, 0.1 $CaCl_2$, 2 Mg_2ATP, 0.5 ethylene glycol-bis (β-amin-ethylether)-N,N,N',N'-tetra-acetic acid (EGTA), 10 N-2-hydroxy ethylpiperazine-N'-2-ethanesulfonic acid (HEPES). The pH of the internal solution was adjusted to 7.25 with KOH. Apamin (300 nM) and charybdotoxin (CTX, 20 nM) were made up to the final concentration in ACSF immediately before use from aliquots of frozen stock solutions, and were administered to the bath through a gravity fed line. At these concentrations both apamin and CTX were reported to specifically block calcium-activated potassium channels without affecting other types of K^+ conductances (Pineda et al, 1992). The high affinity of apamin and CTX for their respective channels made it difficult to wash out the drug, so only partial recovery toward control values could be obtained. Apamin and CTX were purchased from Sigma Co (St Louis, USA).

Recording procedures

Patch pipettes were pulled from 1.5 mm OD glass tube (Chase, USA) using a vertical microelectrode puller (PP83, Narishige, Japan). Pipettes were polished using a microforge (MF83, Narishige), and positioned using hydraulic micromanipulators (Narishige). Recording electrodes were not coated and had 2~3 MΩ of resistance in recording solution. Recordings were carried out using an Axopatch 1D amplifier (Axon Instruments, USA). Recordings were obtained by patching onto cells with clear, nongranular cytoplasm. High-resistance seals were obtained by moving the patch electrode onto the cell membrane and applying gentle suction. After formation of a high-resistance seal between the electrode and the cell membrane, transient currents caused by pipette capacitance were electronically compensated by the circuit of the Axopatch 1D amplifier. If the seal resistance dropped below 1 GΩ during the recording, the experiment was terminated. Immediately after the whole-cell configuration was attained, resting membrane potential was read off the amplifier. The value of the resting potential was monitored regularly throughout the recording, and if significant changes were observed, recordings were terminated. All experiments were carried out at the room temperature (20~25°C). Data after filtration at 5 KHz by low-pass filter were acquired with Digidata 1200 interface and pCLAMP software (Version 6.0.3, Axon instruments, USA) and analyzed with pCLAMP. Results are expressed as the mean±SEM.

RESULTS

Characterization of type A and type B MVN neurons

Eight of 47 neurons (17%) did not show spontaneous activity and had stable resting membrane potentials ranging from −43 mV to −51 mV. The remaining 39 cells were spontaneously active and had resting potentials ranging from −45 mV to −65 mV. The action potential shapes of two typical mature

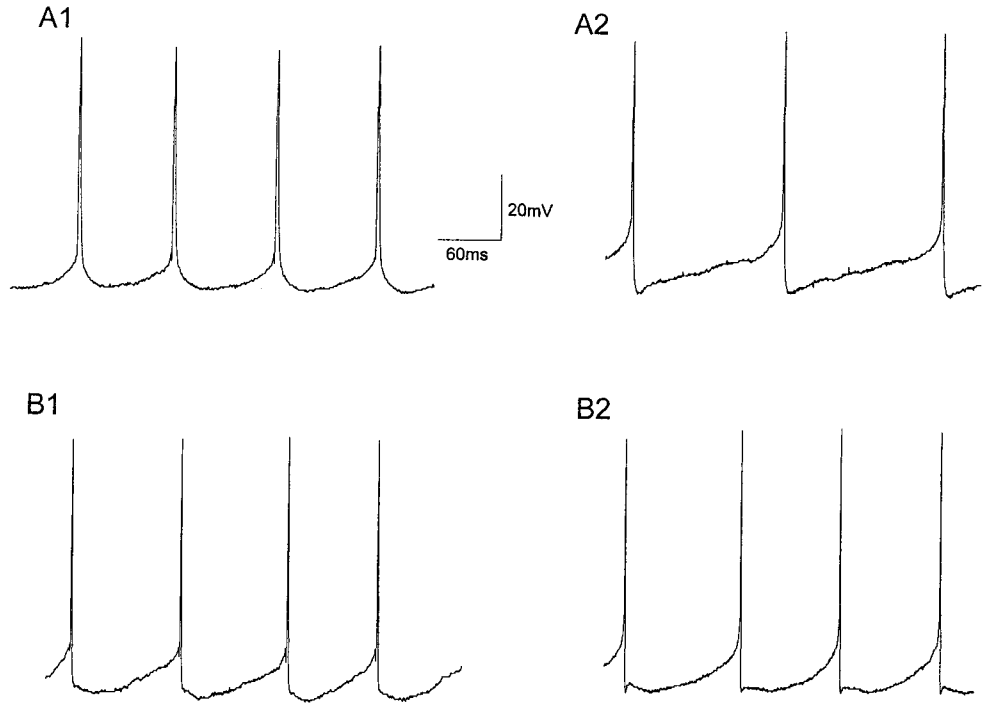

Fig. 1. Action potential shapes of type A and type B MVN neurons. (A1) a typical immature type A cell recorded from a 13-day-old rat. (A2) a typical mature type A cell recorded from a 16-day-old rat. Note the single deep AHP characteristic of type A cells. (B1) a typical immature type B cell recorded from a 14-day-old rat. Note the period of isopotentiality followed by the delayed slow AHP. (B2) a typical mature type B cell. Both the early fast AHP and the delayed slow AHP are present.

MVN neurons (15～17-day-old) are illustrated in Fig. 1 A2 and B2. Fig. 1 A2 was seen to have a single deep AHP following the repolarizing phase of their action potential, and was therefore identified as type A cells. B2 showed both an early fast and a delayed slow AHP, characteristic of type B cells. As shown in Fig. 2, type A and type B cells differed significantly in their mean AHP amplitudes (14.4±1.1 mV and 9.0±1.0 mV, respectively, $p<0.01$), and in their durations of action potential (6.4±0.5 ms and 4.6±0.6 ms, respectively, $p<0.05$). As shown by the spike shapes of immature MVN neurons (P13～14) illustrated in Fig. 1 A1 and B1, the spontaneous action potentials of immature cells differed from the characteristic mature cells in several aspects. In immature type A cells, the majority of cells had broad spike, with a mean duration of 8.4±1.3 ms, followed by a single uniform AHP, and had smaller AHP amplitude than mature type A cells (Fig. 1, 2). Some immature cells at P13～14 had relatively narrower spikes (mean duration, 6.7±0.9 ms; Fig. 2C) than immature type A cells, and characteristically showed a short period of isopotentiality following the repolarizing phase of the action potential followed by a delayed slow AHP. These cells were assumed to be immature type B cells.

Effects of CTX on MVN neurons

Six of eight type A cells and 10 of 11 type B cells were affected by CTX, a well characterized BK_{Ca} channel blocker. Examples of the effects obtained are depicted for two neurons in Fig. 3. The addition of 20 nM CTX to the bathing solution resulted in a reduction in the hyperpolarization after the spike. So spike frequency of both types of MVN cell was increased. To quantify this change in spike frequency, we calculated the increase in firing rate in the presence of the blocker normalized to the firing rate when no blocker was added. The mean increase in type A cells was 42±19% (n=6), and in type B cells it was 31±12% (n=8). Also, spike width was affected

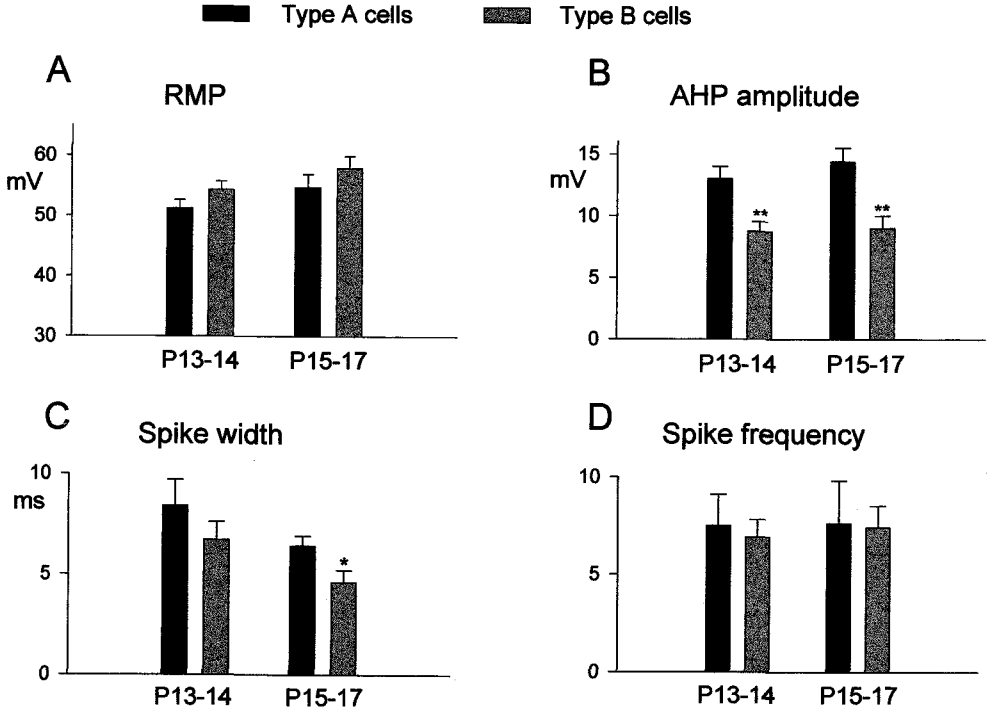

Fig. 2. Membrane and action potential characteristics of type A and type B cells at different ages. The resting membrane potential, AHP amplitude, action potential duration and firing frequency of type A and type B cells at different ages indicated. At 13～14 days, almost all the cells were either immature type A or immature type B cells, while at 15～17 days a majority of cells were mature type A or type B cells. Values are means± SEM. * and ** indicate $p<0.05$ and $p<0.01$, respectively, compared with type A cells.

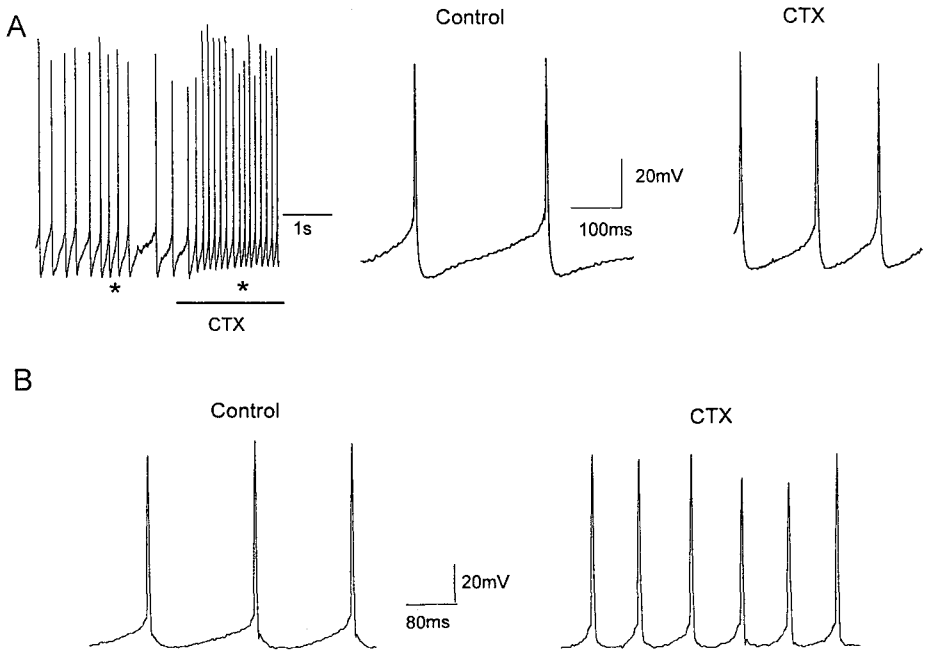

Fig. 3. Effects of CTX on MVN neurons. (A) Application of CTX (20 nM) increased firing frequency of type A cell. The middle and right traces are taken from the left records (*) and displayed at an expanded time scale. (B) effects of CTX on type B cell. Application of CTX induced a reduction of AHP amplitude and increased firing frequency.

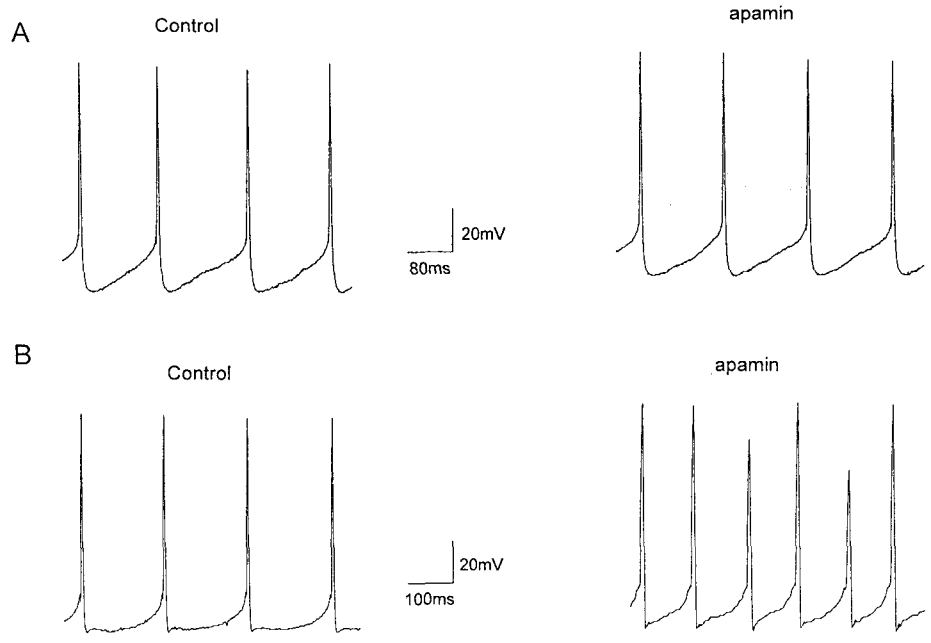

Fig. 4. Effects of apamin on MVN neurons. (A) effects of apamin on type A cell. Apamin has little effects on the spontaneous tonic discharge and the spike shape. (B) effects of apamin on type B cell. Apamin eliminated the delayed slow AHP and increased firing rate.

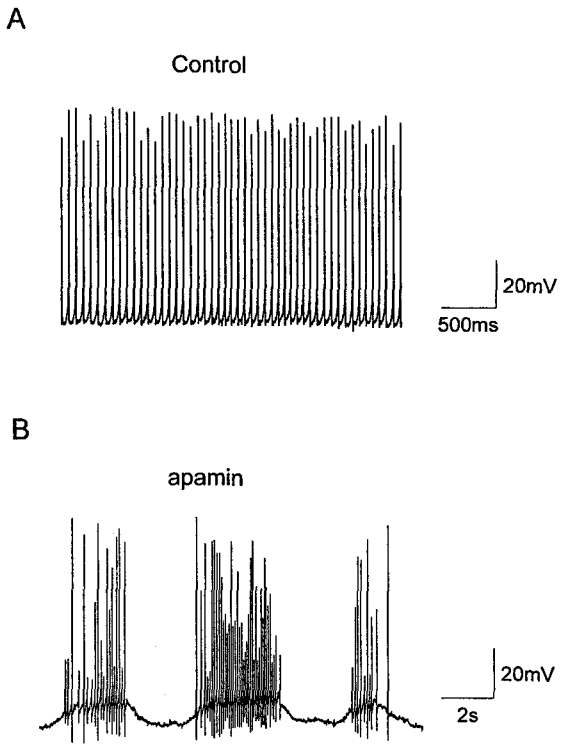

Fig. 5. Effects of apamin on spontaneous activity of type B MVN neuron. (A) resting discharge in ACSF. (B) after 2 min in apamin containing solution. Note the loss of regular spontaneous discharge and the appearance of burst firing.

by CTX with values of 6.9±1.1 ms and 9.2±1.3 ms in the absence and the presence of the blocker, respectively, in type A cells, and 5.4±0.7 ms and 8.0 ±1.2 ms in type B cells. In both type A and B cells, CTX did not induce bursting activity.

Effects of apamin on MVN neurons

The effects of apamin, SK_{Ca} channel blocker, were examined on 5 type A neurons. As shown in Fig. 4A, action potential duration and spike frequency of type A cells were little affected by 300 nM apamin. By contrast, in all 12 type B cells tested, bath application of apamin resulted in a rapid and large increase in the spontaneous firing rate (Fig. 4B). As illustrated, the delayed slow AHP was completely eliminated, whereas the early fast AHP persisted. The spike width was affected by the application of apamin with values of 5.1±0.8 ms and 6.3±0.8 ms in the absence and the presence of the blocker, respectively. After a delay of 1~3 min, a rhythmic burst firing pattern occurred in 10 of the 12 neurons (Fig. 5). This apamin-induced bursting discharge was composed of a train of fast action potentials superimposed on depolarizing plateau lasting 1~3 sec.

DISCUSSION

In the present study we provide evidence that intrinsic membrane properties may play a role in the spontaneous activity generated by MVN neurons. Previously, we demonstrated that postnatal rat MVN neurons express two types of Ca^{2+}-activated K^+ conductances (Chun et al, 1999), with properties similar to those described for BK_{Ca} and SK_{Ca} channels documented in other neurons (Blatz & Magleby, 1987). Here we showed that both apamin- and CTX-sensitive channels are important factors in determining the excitability and rhythmicity of the MVN neurons.

In the present study, the mean resting membrane potentials and AHP amplitudes (Fig. 2) were similar to those in young rat MVN neurons (Johnston et al, 1994). Fig. 2D showed that isolated MVN neurons yielded spike discharges with lower frequency than those obtained from the intact neurons in vivo (Darlington et al, 1995). Most likely, this reflects the fact that recordings from the isolated cells were done at room temperature, while those from the intact MVN were carried out close to body temperature. It is also possible that the loss of dendrites in the isolated cells contributed to this difference. The increase in negativity of the resting membrane potential and the shortening of the spike width in MVN neurons over P15 are analogous to those seen in CA1 pyramidal cells (Costa et al, 1991), cortical neurons (McCormick & Prince, 1987) and dorsal lateral geniculate cells (Ramoa & McCormick, 1994). While changes in chloride extrusion mechanisms and the activity of the Na pump have been implicated in increasing the membrane resting potential of hippocampal pyramidal neurons (Fukuda & Prince, 1992), the development of AHP over the same period in MVN cells suggests that changes in the density or the activation and inactivation kinetics of membrane K conductances may also be involved (Harris et al, 1988; Lockerly & Spitzer, 1992). Similarly, the shortening of the action potential duration in MVN neurons after 15-day-old may reflect changes in Na^+ channel density as in rat hippocampal pyramidal cells

(Fukuda & Prince, 1992).

Apamin-sensitive Ca^{2+}-activated K^+ (K_{Ca}) conductances, mediated by small conductance K_{Ca} channels (Blatz & Magleby, 1987), have been shown to contribute to the medium or intermediate AHP in a number of different neurons, and to play a major role in determining their instantaneous firing rate (Schwindt et al, 1988; Viana et al, 1993). On the other hand, CTX- and TEA-sensitive K_{Ca} conductances, mediated by large conductance K_{Ca} channels (Adams et al, 1982), are typically involved in action potential repolarization and contribute to the fast AHP immediately after a spike (Pineda et al, 1992; Viana et al, 1993).

Application of both apamin and CTX altered spontaneous activities of MVN neurons. However, there were significant differences in firing patterns. In all type B cells tested, application of apamin induced a rapid reduction of delayed AHP amplitude associated with an increase in spontaneous firing rate. These results are in accordance with previous studies which have demonstrated that apamin selectively blocked part of post-spike AHP in a variety of excitable cells (Bourque & Brown, 1987; Schwindt et al, 1988). In addition, these data confirm that the delayed slow AHP in type B neurons is partially mediated by an SK_{Ca} conductance. In contrast to type B neurons, type A MVN neurons was not affected by apamin. These results are in agreement with previous finding in the adult rat (Johnston et al, 1994) and confirm that type A MVN neurons are mainly characterized by the presence of a large single AHP, which mediated by a BK_{Ca} conductances, and an A-like current (Serafin et al, 1991). One to three minutes after adding apamin to the bath, type B neurons exhibited rhythmical bursts. Apamin-induced bursting activity in type B neurons is similar to that reported in guinea-pig type B MVN cells at hyperpolarized membrane potentials (de Waele et al, 1993). Interestingly, in a previous study of the intrinsic properties of MVN neurons, Serafin et al (1991) have proposed type B MVN neurons correspond to the phasic vestibular cells originally described in vivo by Shimazu & Precht (1965). In both types of MVN cells, application of CTX induced a reduction of the early fast AHP and increased spontaneous firing rate, but did not induce rhythmical burst. Similar divergent effects were obtained in retinal ganglion cells where CTX enhanced the firing frequency of these neurons, while apamin induced irregular bursting (Wang et al, 1999). The functional significance of the rhythmic firing pattern is still speculative. A rhythmic bursting of central vestibular neurons in phase with limb extensor activity has been described in cats during fictive locomotion (Orlovsky, 1972). Because we showed in the present study that bursts or plateau potentials are triggered by apamin application, the movement-correlated burst of action potentials might result from the blockade of SK_{Ca} channel of vestibular nucleus neurons. Also, we can speculate that neuromodulators that are known to be able to block the Ca^{2}- dependent K^+ conductances (Nicoll et al, 1990) could play a role in this respect.

In summary, there are differential roles of apamin and CTX sensitive potassium conductances in spontaneous firing patterns of MVN neurons, and these conductances are important in regulating the intrinsic rhythmicity and excitability.

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