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RESEARCH ARTICLE

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Highly 4-aminopyridine sensitive delayed rectifier current modulates the excitability of guinea pig cerebellar Purkinje cells

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Abstract The effects of low concentrations of 4-aminopyridine (4-AP) on the membrane properties of guinea pig cerebellar Purkinje cells were investigated in slice preparation using intracellular recordings. It was found that 1–10 μM 4-AP did not affect the resting potential or the input resistance of the cells, but reduced markedly the duration of the slowly depolarizing potential (SDP), and thus the latency to the firing of Ca^{2+} spikes in response to intracellular current pulses. Intradendritic recordings in the presence of tetrodotoxin, Cd^{2+}, and low $[Ca^{2+}]_o$, which blocked all the regenerative responses, exhibited prominent membrane outward rectification in response to depolarizing current pulses. Under these conditions, the SDP was abolished and, in contrast, a slowly developing hyperpolarization was consistently observed. Application of 10 μM 4-AP reduced the outward membrane rectification in a reversible manner, but did not affect the transient hyperpolarization, which is usually attributed to the activation of potassium "A'' current. These results demonstrate, for the first time, the presence of a highly 4-AP sensitive delayed rectifier in guinea pig cerebellar Purkinje cells, which prominently affects their excitability. The results also indicate that the slowly depolarizing potential of guinea pig Purkinje cells does not involve inactivation of transient potassium currents, which has been suggested previously as an underlying mechanism for this phenomenon in turtle Purkinje cells.

Keywords Cerebellum · Potassium channels · 4-Aminopyridine · Dendritic recording

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Introduction

A long latency to the firing of Ca^{2+} spikes, following the onset of a depolarizing pulse, is one of the complex electrophysiological properties of Purkinje cells, which was initially observed in guinea pig (Linnas and Sugimori 1980a, 1980b), and studied more extensively in the turtle cerebellum (Hounsgard and Midtgaard 1988; Midtgaard et al. 1993). During this period, Purkinje cells display a slowly depolarizing potential (SDP) of variable duration, which influences the dendritic Ca^{2+} influx and postsynaptic responses on a time scale of several seconds (Midtgaard et al. 1993; Midtgaard 1995). In the turtle, this latency was eliminated in the presence of 2–5 mM 4-aminopyridine (4-AP), and therefore has been attributed to a slow inactivation of dendritic "A"-like transient potassium current. The precise characterization of outward currents in Purkinje cells has been largely limited (Gruol et al. 1991). However, in the somatic region the transient outward current of mammalian Purkinje cells resembles kinetically and pharmacologically the typical fast "A" current in other neurons (Wang et al. 1991).

Recently, we have reported that 4-AP in concentrations as low as 1–10 μM prominently affects the pattern of sustained Ca^{2+} spike firing in guinea pig Purkinje cells (see Fig. 1B). These results have led us to suggest that the aforementioned interpretation of the effects of 2–5 mM 4-AP in turtle should be reevaluated (Etzion and Grossman 1998).

Although the underlying mechanism of the SDP may not be identical in different species, the close resemblance in the firing properties of turtle and guinea pig Purkinje cells (Hounsgard and Midtgaard 1988), as well as the similarity in their response to changes of $[K^+]_o$ or application of 2–5 mM 4-AP (Etzion and Grossman 1998), strongly suggests a similar underlying mechanism.

Recent reports, which indicate the involvement of 4-AP sensitive current in learning-specific changes of dendritic membrane excitability in Purkinje cells (Schreurs et al. 1997, 1998), emphasize the crucial importance of such reevaluation.

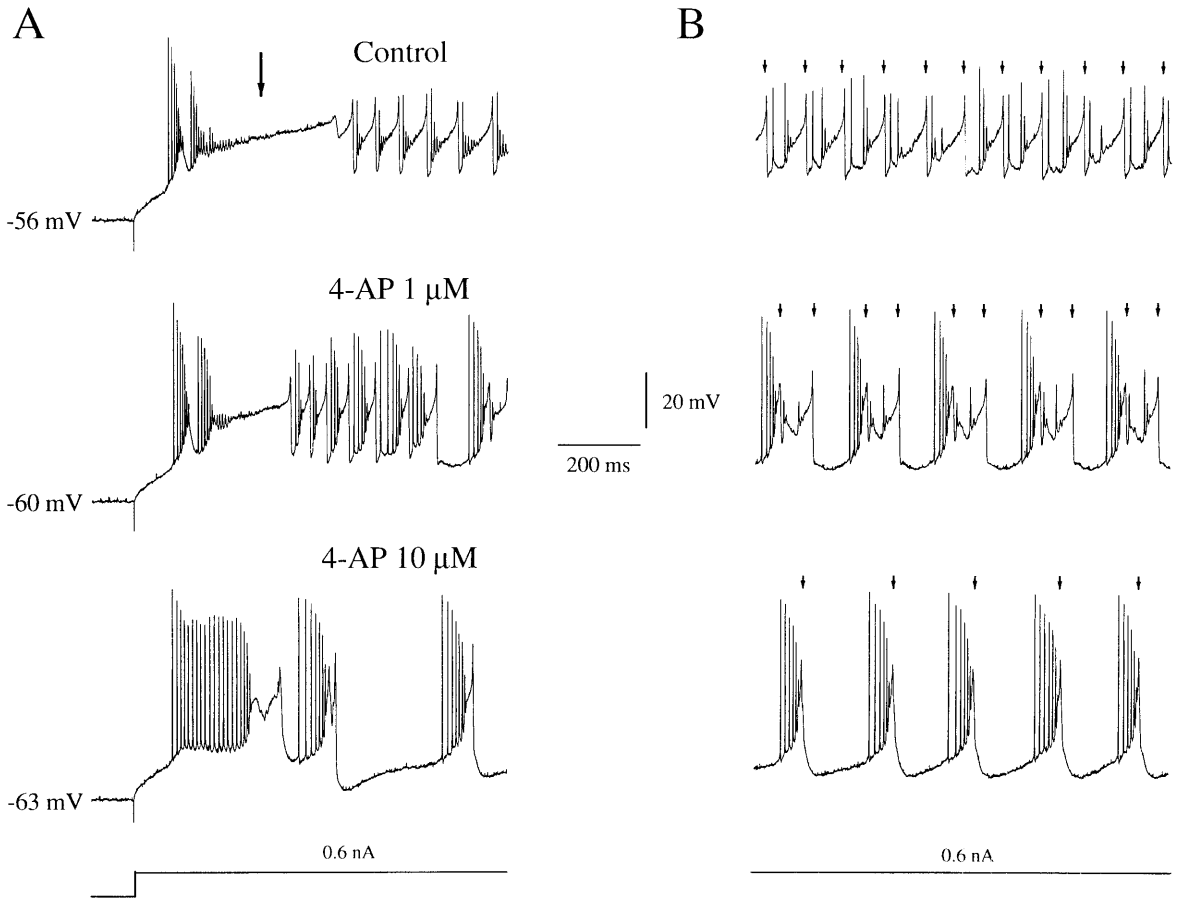

Fig. 1A, B 4-Aminopyridine modification of SDP and Ca^{2+} spike firing pattern. **A** Somatic recordings. Under control conditions this cell demonstrated SDP (*arrow*) with a latency of approximately 500 ms to the firing of Ca^{2+} spikes. This latency was progressively decreased in the presence of 1 and 10 μM 4-AP (*lower traces*). **B** Segments of the corresponding recordings in **A**, 3 s after the onset of the depolarizing pulse. Note that the regular Ca^{2+} spike firing (*arrows*) under normal conditions turns into a doublet pattern in the presence of 1 μM 4-AP, and then is modified to large single spikes followed by prominent AHPs, under 10 μM 4-AP conditions (see Etzion and Grossman 1998)

The present experiments, which extend our previous findings, were designed to study the properties of the highly 4-AP sensitive response of Purkinje cells, without the interference of Na^+ and Ca^{2+} currents. We demonstrate that under these conditions the SDP is abolished, and application of 1–10 μM 4-AP blocks a delayed rectifier potassium current, without affecting the conventional "A" current. This novel potassium current prominently affects the excitability of guinea pig Purkinje cells.

Materials and methods

Three-hundred-micrometer-thick sagittal cerebellar slices were cut from adult male albino guinea pigs (200–650 g) under pentobarbitone sodium anesthesia (Nembutal 40 mg/kg) as previously described (Etzion and Grossman 1998, 1999), and according to the animal use guidelines of the Council of the American Physiological Society. The slices were incubated at room temperature for at least 1 h before recording in oxygenated (95% O_2 and 5% CO_2) Ringer's solution (in mM: NaCl 124, KCl 5, NaH_2PO_4 1.25, $MgSO_4$ 2, $NaHCO_3$ 26, $CaCl_2$ 2, and glucose 10).

After the incubation period, single slices were transferred to a recording chamber (2 ml volume), and superfused continuously with oxygenated Ringer's solution preheated to 30°C (TC-324B, Warner). The Ringer's solution was applied to the recording chamber by a peristaltic pump (Masterflex; 7518–10) at a flow rate of 5–7 ml/min. 4-AP (1–10 μM; Sigma) was added to the Ringer's solution immediately before use. Na^+ and Ca^{2+} currents were blocked by Ringer's solution containing tetrodotoxin (TTX, 0.5 μM; Sigma), $CdCl_2$ 0.2 mM, $MgCl_2$ 1.5 mM and $CaCl_2$ 0.2 mM (Na^+, Ca^{2+} block solution). Intracellular voltage recordings were performed using 4 M potassium-acetate-filled sharp electrodes (electrode resistance, 50–120 MW) with a bridge balance amplifier (Axoprobe-1A, Axon). Intradendritic recordings from Purkinje cells were obtained by advancing the microelectrode (MP-285 manipulator, Sutter Instruments) to the central part of the molecular layer under direct visual control (Zeiss-Axioskop, ×100). The effects of 4-AP under normal conditions were studied either in cells with stable resting potential (below –55 mV) or in spontaneously active cells whose oscillations were suppressed by hyperpolarizing d.c. injection (up to 1 nA). The hyperpolarizing holding current was kept constant during these experiments, and the bridge balance was monitored to avoid incorrect measurements of the resting potential. In the experiments in which Na^+, Ca^{2+} block solution was applied prior to the application of 4-AP, spontaneous firing ceased 5–10 min after perfusion with the Na^+, Ca^{2+} block solution. Therefore, hyperpolarizing d.c. injection was not used in these experiments.

Intracellular recordings were filtered (5–10 kHz), digitized (National Instruments board; AT-MIO-16D), and stored on PC disk. Data acquisition and analysis were performed using self-programmed software (Labview 3.0.1; National Instruments). Statistical analysis was performed with Student's paired *t*-test. The data in the text and figures are expressed as means ± SEM.

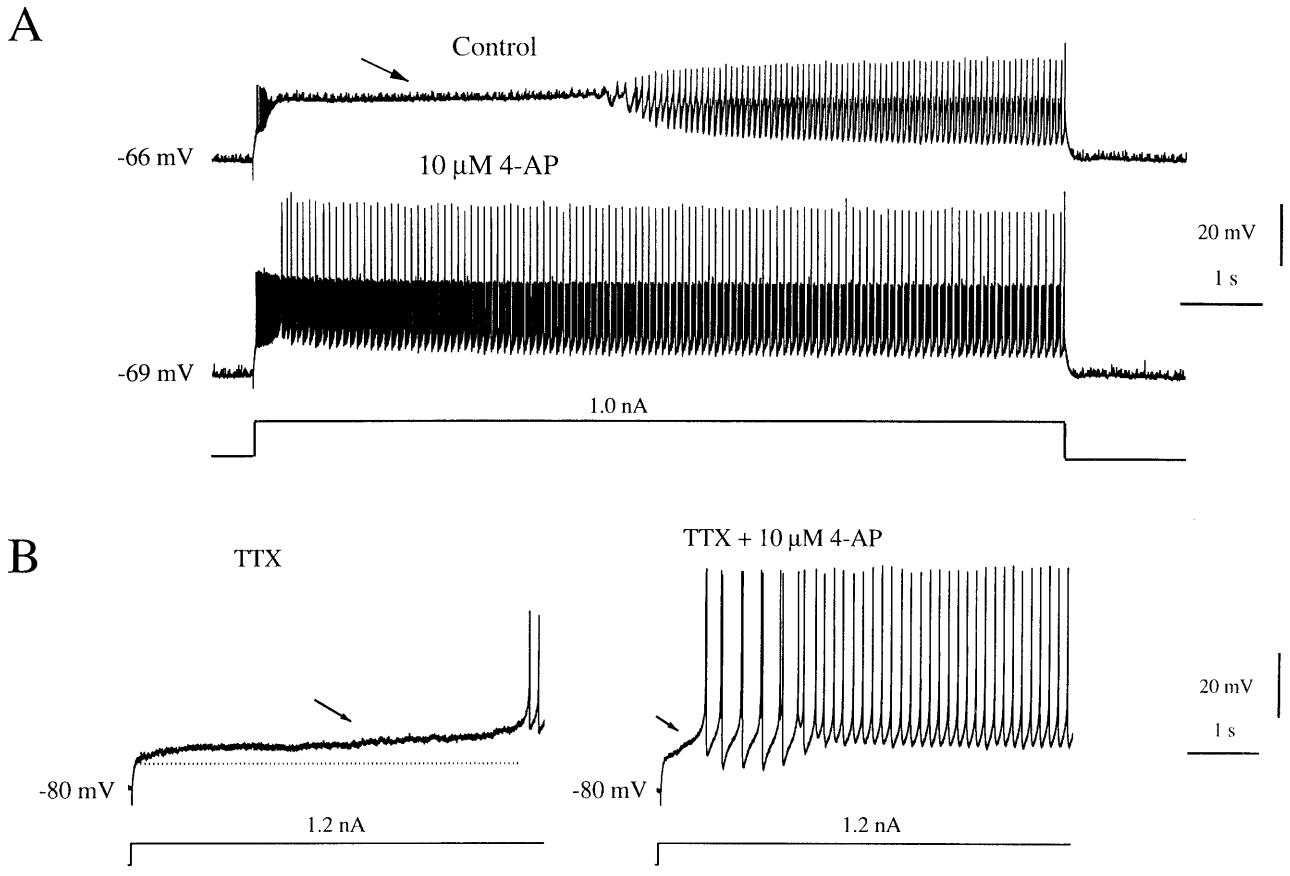

Fig. 2A, B 4-Aminopyridine effect on prolonged SDP. **A** Dendritic recordings. Under control conditions an SDP with a latency of approximately 3 s to the firing of Ca^{2+} spikes is observed (*arrow*). Application of 10 µM 4-AP almost abolished this SDP. **B** Dendritic recording (different cell from **A**) in the presence of 0.5 µM TTX. SDP with a latency of approximately 5 s to the firing of Ca^{2+} spike (*left trace*) is reduced to less than 1 s upon application of 10 µM 4-AP

Results

Low concentrations of 4-AP shorten the SDP

Previous studies which concentrated on the SDP of Purkinje cells were performed on the turtle cerebellum (Hounsgard and Midtgaard 1988; Midtgaard et al. 1993; Midtgaard 1995). Both somatic and dendritic recordings in the present study demonstrate similar SDP in guinea pig cerebellar Purkinje cells. As in the turtle cerebellum, this phenomenon was highly variable in its duration, and was observed in the absence or the presence of TTX (Figs. 1, 2). Addition of 1–10 µM 4-AP consistently decreased the duration of the SDP, but this effect was most prominently noted in cells which displayed very long (seconds) SDP (Fig. 2). In nine similar experiments, in which cells exhibited SDP in a range between 280 ms and 6780 ms, 4-AP significantly reduced its duration to 39.9±9.4% of control (P=0.002). This effect occurred without a significant change in the resting potential (control: –67.3±3.0 mV vs 4-AP treated: –68.4±3.2 mV, P=0.44) or the input resistance of the recorded cells (control: 23.4±3.9 MW vs 4-AP treated: 21.9±3.7 MW, P=0.22). In two recordings the effect of 4-AP on the slowly depolarizing potential of several seconds was so prominent that it could be clearly noted even when the injected current was decreased to less than one-third of its value under normal conditions. Moreover, in other recordings in which TTX (0.5 µM) and Cd^{2+} (200–400 µM) were applied and $[Ca^{2+}]_o$ was kept normal (n=2), regenerative responses were apparently blocked, but application of 10 µM 4-AP resumed the capability of the cells to generate slow regenerative responses, probably by unmasking residual Ca^{2+} currents (not shown). These results emphasize the increased excitability of Purkinje cells in the presence of 1–10 µM 4-AP. It should be noted that in some recordings a prominent effect on the SDP was apparent 10 min after drug application. In time control experiments, in cells that were maintained for 30–90 min under normal conditions, shortening of the SDP was never observed. Therefore, the possibility of non-specific drift of this property due to extended recording periods is highly unlikely.

Blockage of Na^+ and Ca^{2+} currents reveals outward rectification and eliminates the SDP

In order to reveal the source of the SDP and the effects of low concentrations of 4-AP, cells were recorded in Na^+, Ca^{2+} block solution. These recordings were per-

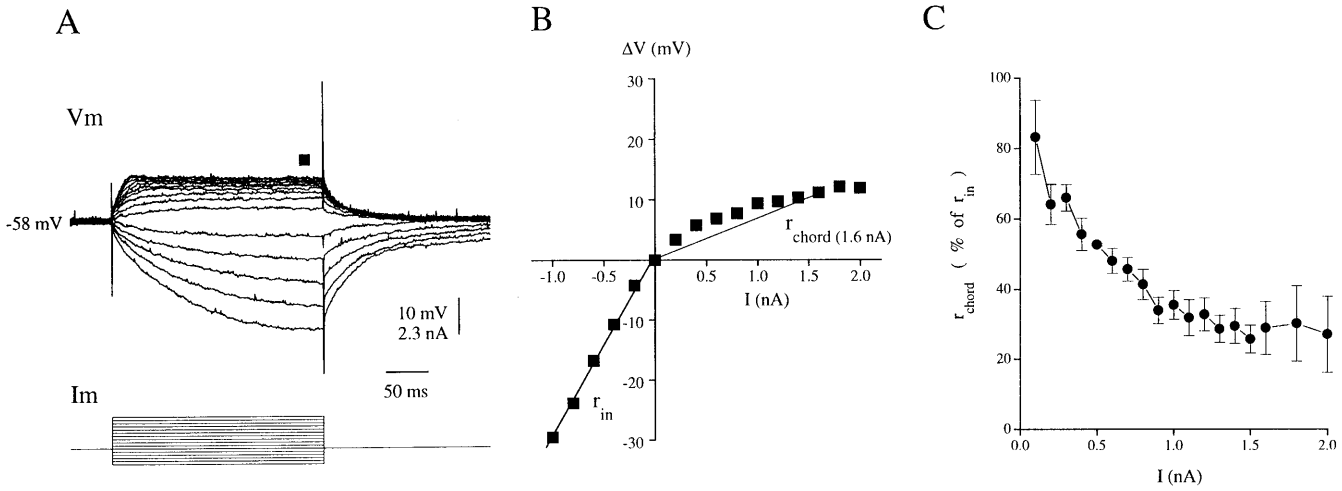

Fig. 3A–C Membrane outward rectification in the dendrites after Na^+ and Ca^{2+} currents are blocked. **A** Marked rectification in response to depolarizing pulses is evident. **B** V-I curve of the cell presented in **A**. Time of measurement is indicated in **A** by *the corresponding symbol*. An example of chord resistance (r_{chord}) for a depolarizing current of 1.6 nA is shown. **C** Averaged data of ten dendritic recordings. r_{chord} is normalized as a percentage of r_{in} for each cell, and plotted as a function of the depolarizing current pulses. Note the prominent reduction of r_{chord} as the depolarizing current is increased

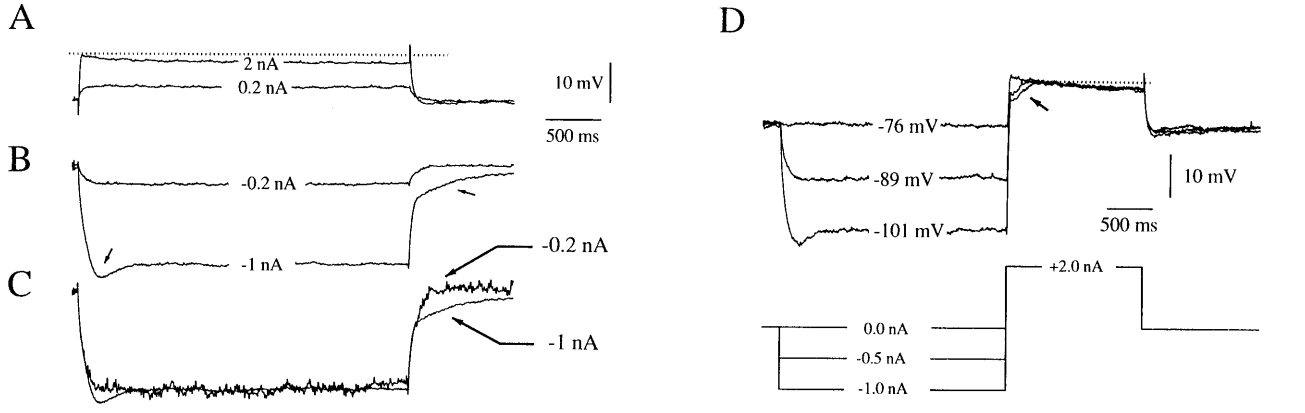

Fig. 4A–D Dendrites do not display SDP when Na^+ and Ca^{2+} currents are blocked. **A–C** Same cell as in Fig. 3A. Response to long (3-s) depolarizing and hyperpolarizing pulses. **A** Persistent rectification is noted in the presence of depolarizing pulses. Note the absence of SDP. In contrast, the response to the 2-nA current pulse is slowly decaying. **B** During the hyperpolarizing pulse a "sag" in the initial phase (*left arrow*) and a "transient hyperpolarization" in the relaxation phase (*right arrow*) of the hyperpolarizing response to –1.0 nA are observed. **C** The "sag" and the "transient hyperpolarization" are clearly distinguished when the response to –0.2 nA is normalized to the same size as the response to –1.0 nA. Note that the transient hyperpolarization lasts no longer than a few hundred milliseconds. **D** Another cell. Preconditioning hyperpolarizing pulses prior to a test pulse of +2.0 nA increased the observed transient hyperpolarization (*arrow*) but did not affect the decay phase. Current intensities (nA) and membrane potentials (mV) are indicated on the appropriate traces

formed from the Purkinje cell dendrites where Ca^{2+} spikes that are affected by 4-AP, originate. As noted above ("Materials and methods"), hyperpolarizing d.c. was not used in these recordings, and spontaneously active Purkinje cells ceased firing a few minutes after application of the Na^+, Ca^{2+} block solution. Recordings were started after 15 min when all of the cells maintained a stable membrane potential (average 61.2± 3.1 mV, n=10) and did not display regenerative responses following depolarization. Under these conditions, current pulses of short (250 ms) duration were initially injected. These short pulses did not induce the prominent sag or transient hyperpolarization that was observed with longer pulses (see below), and therefore enabled precise bridge balancing. The V-I curve of each cell was obtained, and the input resistance (r_{in}) was calculated from the responses to the hyperpolarizing pulses (average 22.3±1.8 MΩ). In all neurons, prominent outward rectification was noted when depolarizing current pulses were injected (Fig. 3A, B). To quantify this phenomenon, chord resistance (r_{chord}) was measured (see example in Fig. 3B) for all the depolarizing responses in each cell, and presented as percentage of the r_{in} in the same cell. The normalized responses of all the dendrites (Fig. 3C) clearly show an exponential decay of the r_{chord} as the depolarizing current is increased (64.1±5.6%, 41.3±4.3% and 28.9±7.6% at 0.2 nA, 0.8 nA and 1.6 nA, respectively). The rectification was persistent and clearly noted also at the end of long (3-s) depolarizing current pulses (Fig. 4A).

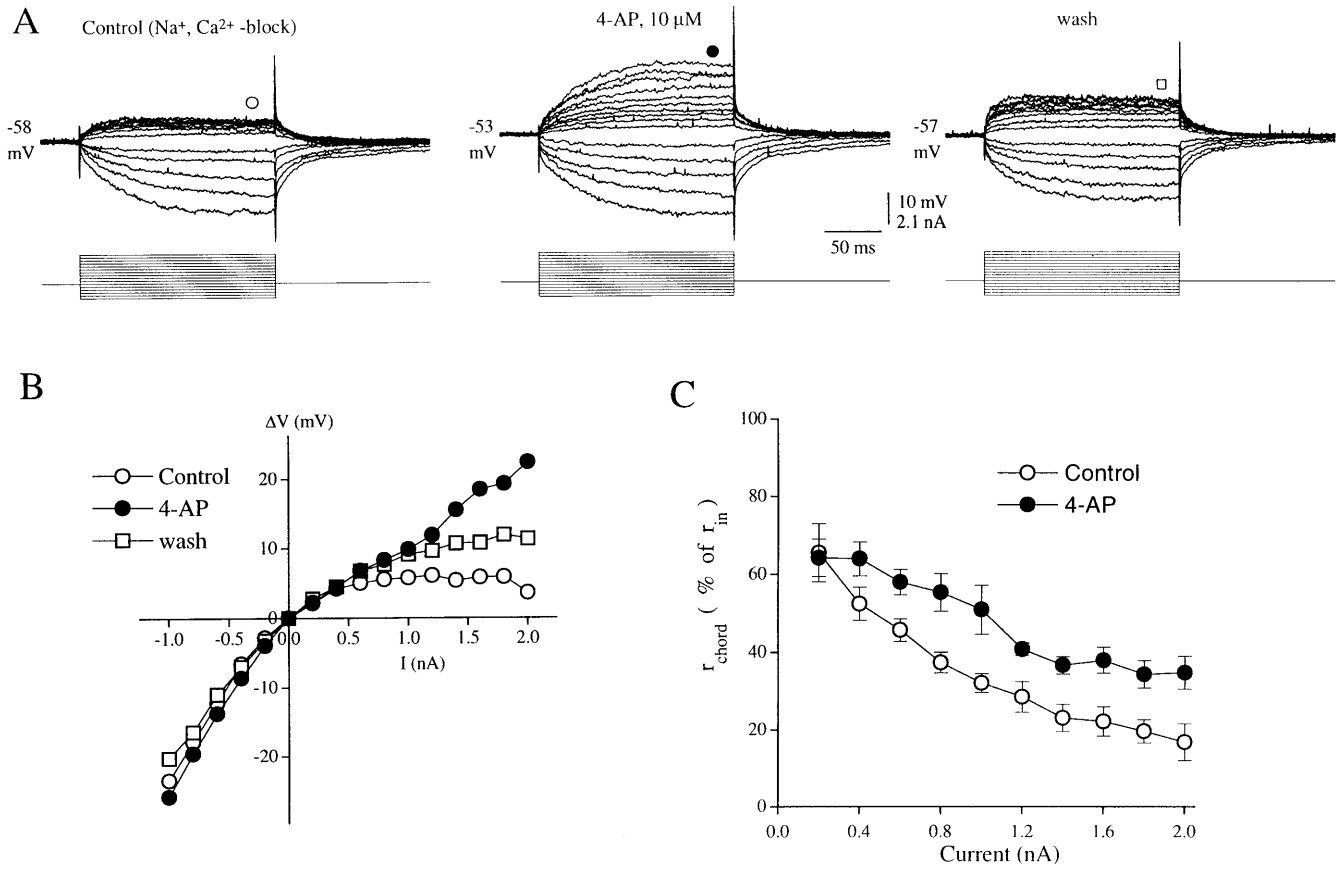

Fig. 5A–C Membrane outward rectification is reduced in the presence of 10 µM 4-AP. **A** Response to short (250-ms) pulses in the presence of Na^+ Ca^{2+} block solution (Control), 30 min after 10 µM 4-AP was applied, and 15 min after washout of the drug. Note the reversible marked decrease of the rectification. **B** V-I curves of the recordings in **A**. **C** r_{chord} as a function of depolarizing current before and after 10 µM 4-AP application (n=7 for 0.2–1 nA, n=5 for 1.2–1.4 nA, and n=3 for 1.6–2.0 nA). 4-AP significantly increased the r_{chord} for the maximal injected current to 235.7±61.9% of the control value (P<0.05, n=7). Time of measurement is indicated in **A** by *the corresponding symbols*

If inactivating K^+ conductance(s) are involved in the generation of the SDP, then blockage of inward currents should not entirely abolish it (Nisenbaum et al. 1994). However, in the present experiments the SDP was completely abolished and, in contrast, the response to the maximal depolarizing injected current (1.2–2 nA) was significantly hyperpolarized at 1 s and 2.8 s compared to the response at 200 ms (81.2±3.1% and 74.4±5.1%, respectively, n=10, P<0.01 for both). The response to long hyperpolarizing pulses (Fig. 4B) exhibits the sag in the initial phase and transient hyperpolarization in the relaxation phase, which were both previously described in detail (Crepel and Penit-Soria 1986; Hounsgaard and Midtgaard 1988). These two components are observed more clearly when the response to –0.2 nA is normalized and superimposed on the response to –1 nA (Fig. 4C). It should be noted that, as in this example, the transient hyperpolarization always lasted only a few hundreds of milliseconds. In order to evaluate whether the absence of SDP under these conditions results from resting inactivation of slow transient potassium current, hyperpolarizing conditioning pulses were given prior to the depolarizing test pulse (Fig. 4D). This protocol increased the "normal" transient hyperpolarization of short duration (Fig. 4D, arrow), but did not change the general course of the voltage response, which exhibited a slowly hyperpolarizing response as noted without the conditioning pulses (Fig. 4A).

Reduction of the outward rectification by 10 µM 4-AP

In the presence of Na^+,Ca^{2+} block solution, 10 µM 4-AP was applied in order to evaluate its effects on the membrane properties described above. The responses were measured at least 15 min after 4-AP application. Resting potential and r_{in} were not significantly changed in the presence of the drug (P=0.46 and P=0.38, respectively, n=7), and 10 µM 4-AP significantly decreased the outward rectification (Fig. 5). Partial recovery was observed after 15 min washout of the drug (Fig. 5A, B). Washout was seen even when application of 4-AP preceded the addition of Na^+, Ca^{2+} block solution (not shown). The reduced rectification in the presence of 10 µM 4-AP was persistent when long depolarizing pulses were applied (Fig. 6A). As predicted, at these low concentrations 4-AP did not affect the transient hyperpolarization (Fig. 6B, C).

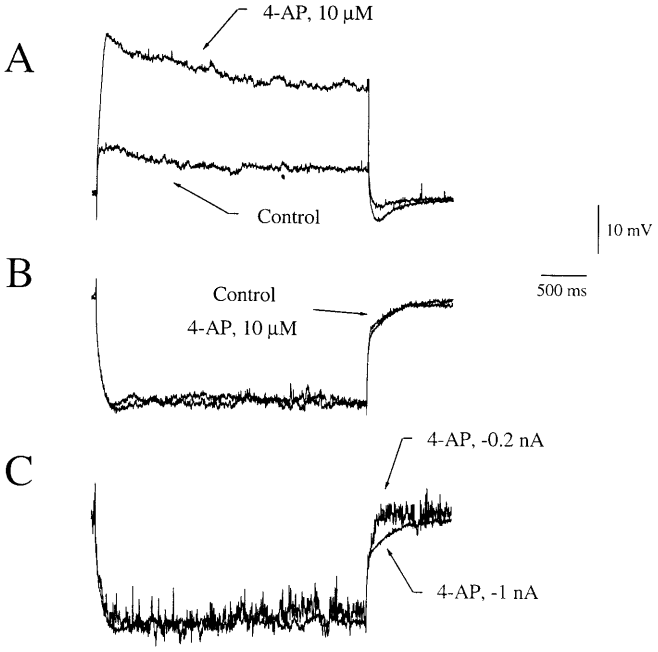

Fig. 6A–C Effect of 10 μM 4-AP on membrane rectification is persistent. **A–C** Same cell as in Fig. 5. Responses to long (3-s) pulses. **A** Voltage response to a current pulse of +1.8 nA. Note the persistent effect of 4-AP on the observed response, as compared to the control response. **B** Voltage response to a current pulse of –1.0 nA. Note the similarity of the voltage responses before and after the application of 4-AP. **C** In the presence of 10 μM 4-AP the "transient hyperpolarization" is clearly observed when the response to –0.2 nA is calibrated to the same size as the response to –1.0 nA, and both are superimposed

Discussion

The SDP

The results of the present study demonstrate that 1–10 μM 4-AP shortens the whole spectrum of SDP, which can last from a few hundreds of milliseconds up to several seconds (Figs. 1, 2). Consequently, the long latency to the firing of Ca^{2+} spikes after the onset of depolarizing pulse is greatly reduced, indicating a general increase in Purkinje cell excitability.

Similar slowly developing depolarization and long latency to the first Ca^{2+} spike, as well as a transient hyperpolarization at the end of hyperpolarizing pulses, were previously described in turtle cerebellar Purkinje cells (Hounsgard and Midtgaard 1988; Midtgaard et al. 1993; Midtgaard 1995). Both responses were attributed to a slowly inactivating "A"-like potassium current.

Another type of latency to a Na^+ spike discharge was described in various CNS neurons such as hippocampal CA1 pyramidal neurons (Storm 1988), dorsal lateral geniculate neurons (McCormick 1991), and neostriatal spiny neurons (Kita et al. 1984). This delayed excitation was dependent on activation of a slowly inactivating, outward current termed I_D which was intermediately sensitive to 4-AP (Storm 1988; McCormick 1991). However, in the neostriatal spiny neurons, for example, a substantial fraction of the SDP was eliminated by blocking inward Na^+ and Ca^{2+} currents, indicating that a slow increase in inward currents (rather than a decrease in outward currents) is responsible for the gradually developing depolarization (Kita et al. 1985; Nisenbaum et al. 1994). Such a mechanism is likely in Purkinje cells since slow plateau-like responses induced by Na^+ and Ca^{2+} currents are prominent in these cells (Llinas and Sugimori 1980a, 1980b). The present results demonstrate that when Na^+ and Ca^{2+} currents are blocked, the slow depolarizing potential of guinea pig Purkinje cells is abolished and, moreover, a slowly developing hyperpolarization is observed. Such a phenomenon is noted even in the presence of preconditioning membrane hyperpolarization, which should eliminate baseline inactivation of transient potassium currents. Furthermore, in our experiments as in those performed in turtle (Hounsgaard and Midtgaard 1988), this procedure induced a substantial amplification of the "normal" transient hyperpolarization (Fig. 4D). We conclude that the slowly depolarizing potential of guinea pig Purkinje cells is completely dependent on the existence of Na^+ and Ca^{2+} currents, and therefore does not involve inactivation of transient potassium currents.

Outward rectification

In current clamp studies, sensitivity to 4-AP is often used as a criterion for identifying a given membrane property as an "A" potassium current. However, some delayed rectifier currents are highly sensitive to 4-AP (Rudy 1988). Along this line we have suggested that the high sensitivity to 4-AP (1–10 μM) of sustained Ca^{2+} spike firing may indeed result from blockage of a non-transient voltage sensitive K^+ current (Etzion and Grossman 1998). In the present study, intracellular dendritic recordings in the presence of Na^+ and Ca^{2+} current blockers displayed prominent outward rectification in response to depolarizing current pulses. This rectification cannot be detected under normal ionic conditions. The significant and reversible effect of 10 μM 4-AP on this rectification is direct evidence that the described effects on the firing properties of Purkinje cells reflect blockage of non-transient voltage dependent K^+ current. Recent studies, of various CNS neurons, have shown delayed rectifier currents which are sensitive to submillimolar concentrations of 4-AP, with indications for the involvement of Kv3.1 and Kv3.2 proteins in the construction of the underlying channels. The properties of these delayed rectifier currents, which include very fast deactivation rates, are thought to contribute to the ability of the involved neurons to fire sustained trains of Na^+ spikes at high frequency (Martina et al. 1998; Rudy et al. 1999). Interestingly, this mechanism has been recently suggested to underlie similar firing properties in isolated cerebellar Purkinje neurons (Raman and Bean 1999). Additional studies are required to determine the exact physiological properties, spatial distribution and molecular

identity of the highly 4-AP sensitive current described in the present study. Our findings indicate that this current influences the slowly depolarizing potential by counteracting the augmentation of inward currents, rather than by a direct effect (slow inactivation). Such a mechanism may explain the huge variability in the duration of the slowly developing depolarization, which is inconsistent with a time course of inactivation of a single potassium current. One major difficulty in the previous attempts to describe the K^+ channels in Purkinje cells was the absence of drugs that can differentiate between the various channels (Gruol et al. 1991). Therefore, the high sensitivity of this delayed rectifier current to 4-AP is an important pharmacological tool for future studies on this issue. The prominent effect of 1–10 μM 4-AP on the dendritic excitability indicates that the novel delayed rectifier described here is an important modulator of dendritic activity. Therefore, this current rather than the "A" current is probably involved in the learning-specific changes of dendritic excitability reported by Schreurs et al. (1997, 1998). The present results, therefore, should also prompt reevaluation of the role transient K^+ currents play in cerebellar Purkinje cells.

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