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Physiological Role of Dendrotoxin-Sensitive K^+ Channels in the Rat Cerebellar Purkinje Neurons

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Summary

To understand the contribution of potassium (K^+) channels, particularly α-dendrotoxin (D-type)-sensitive K^+ channels (Kv.1, Kv1.2 or Kv1.6 subunits), to the generation of neuronal spike output we must have detailed information of the functional role of these channels in the neuronal membrane. Conventional intracellular recording methods in current clamp mode were used to identify the role of α-dendrotoxin (α-DTX)-sensitive K^+ channel currents in shaping the spike output and modulation of neuronal properties of cerebellar Purkinje neurons (PCs) in slices. Addition of α-DTX revealed that D-type K^+ channels play an important role in the shaping of Purkinje neuronal firing behavior. Repetitive firing capability of PCs was increased following exposure to artificial cerebrospinal fluid (aCSF) containing α-DTX, so that in response to the injection of 0.6 nA depolarizing current pulse of 600 ms, the number of action potentials insignificantly increased from 15 in the presence of 4-AP to 29 action potentials per second after application of DTX following pretreatment with 4-AP. These results indicate that D-type K^+ channels (Kv.1, Kv1.2 or Kv1.6 subunits) may contribute to the spike frequency adaptation in PCs. Our findings suggest that the activation of voltage-dependent K^+ channels (D and A types) markedly affect the firing pattern of PCs.

Key words
Potassium channels • Purkinje neurons • Intracellular recording • Firing behavior • α-dendrotoxin

Introduction

The Purkinje cells provide the sole output of the cerebellar cortex. These neurons show spontaneous action potential firing under both *in vivo* (Jaeger and Bower 1994, Williams *et al.* 2002) and *in vitro* conditions (Granit and Phillips 1956, Eccles *et al.* 1967, Llinas and Sugimori 1980, Womack and Khodakhah 2002a,b, 2003, 2004, Cavelier *et al.* 2003, Swensen and Bean 2003), which is generated by intrinsic membrane conductances (Raman and Bean 1997, 1999, Williams *et al.* 2002) and become very regular when synaptic inputs are blocked (Häusser and Clark 1997, Edgerton and Reinhart 2003).

During the past decade, converging lines of evidence suggested that alterations in Purkinje neuronal firing patterns are of considerable physiological importance (Edgerton and Reinhart 2001). These data indicate that changes in the temporal organization of Purkinje neuronal spike trains represent a mechanism through which these neurons alter their influence on

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target cells in the cerebellum. The mechanisms responsible for generation of bursting activity in Purkinje neurons (PCs) are incompletely understood, but are likely to involve both extrinsic and intrinsic components. *In vitro* studies have contributed to our understanding of how Purkinje neuronal firing behavior emerges on a cellular level, and how it can be modulated both acutely and in the long term. Although PCs possess a variety of voltage- and calcium-gated K^+ channels (Raman and Bean 1997, 1999, Sacco and Tempia 2002, Swensen and Bean 2003, McKay and Turner 2004, Womack and Khodakhah 2004), their respective contributions to the electrophysiological properties exhibited by these neurons are incompletely understood. This study was carried out in order to provide a clearer picture of how voltage-dependent K^+ channels (Kv. 1, Kv1. 2 or Kv1. 6) influence Purkinje neuron activity.

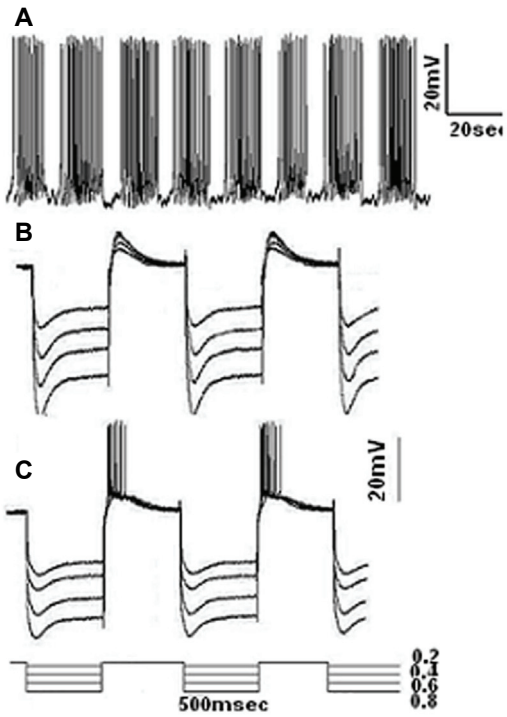

Fig. 1. Spontaneous firing behavior of Purkinje neurons and modulation of rebound responses by K^+ channel. Spontaneous activity of Purkinje neurons under the control condition (A). The membrane hyperpolarization due to 500 ms steps (-0.1 to -0.8 nA) was followed by a depolarizing 'sag'. Typical examples of rebound depolarizations (RD) under the control condition (B) and in the presence of 200 nM DTX (C).

Materials and Methods

All experiments were performed on rat brain slices maintained *in vitro*. Sprague-Dawley rats (male; 15–30 days) were anesthetized by inhalation of ether and then decapitated. These procedures were in accordance with the guidelines of the Institutional Animal Ethics Committee at Shaheed Beheshti Medical Sciences University. The cerebellum was promptly removed and immersed in ice-cold artificial cerebrospinal fluid (aCSF) containing (mM): 124 NaCl, 5 KCl, 1.2 KH_2PO_4, 1.3 $MgSO_4$, 2.4 $CaCl_2$ and 10 glucose bubbled continuously with a mixture of 95 % O_2 and 5 % CO_2. Parasagital slices (300 µm thick) were cut from the cerebellar vermis using a vibroslicer (752 M, Campden Instruments Ltd., Loughborough, UK). The slices were allowed to recover in oxygenated aCSF at 36 ºC for ≥ 1 h, thereafter the recordings were performed in a submersion chamber at room temperature (23-27 ºC) that was perfused with aCSF (pH 7.4; flow rate 2 ml/min) containing 1 mM kynurenic acid and 100 µM picrotoxin to block ionotropic glutamate (Stone 1993) and gamma aminobutyric acid (GABA) (Yoon *et al.* 1993) receptors, respectively. Thus, most of the spontaneous activity can be attributed to the intrinsic properties of the PCs. For recording from slices, a U-shaped platinum-frame nylon net was used to hold the slice in place.

Slices were visualized using an upright microscope using an x40 water-immersion objective lens (BX51WI, Olympus, Japan). Intracellular recordings were made from Purkinje cells (n=66), using conventional glass microelectrodes filled with 3 M potassium chloride (40-80 MΩ), connected to the head stage of an Axoclamp 2B amplifier (Axon Instruments, Foster City, CA, USA). The reference electrode in all experiments was a silver-silver chloride wire within an agar bridge (4 % agar in aCSF). Intracellular potentials were recorded using the active bridge mode of the Axoclamp amplifier. Data were filtered at 30 kHz, voltage records were sampled at 40 kHz and digitized online using a 16 bit A/D converter (ADInstrument Pty Ltd., Sydney, Australia) connected to an IBM-compatible computer and stored for further analysis using Chart 5, Matlab, MiniAnalysis and Excel software. Repetitive firing in response to depolarizing current injection (500 ms) was evaluated by measuring the number of spikes versus the amplitude of injected current (up to 1 nA). The amplitude of the action potential and after hyperpolarization (AHP) was measured relative to this threshold, and the action potential duration was measured at the level of threshold.

Drugs were diluted up to a known concentration in aCSF and applied to the slice by switching the

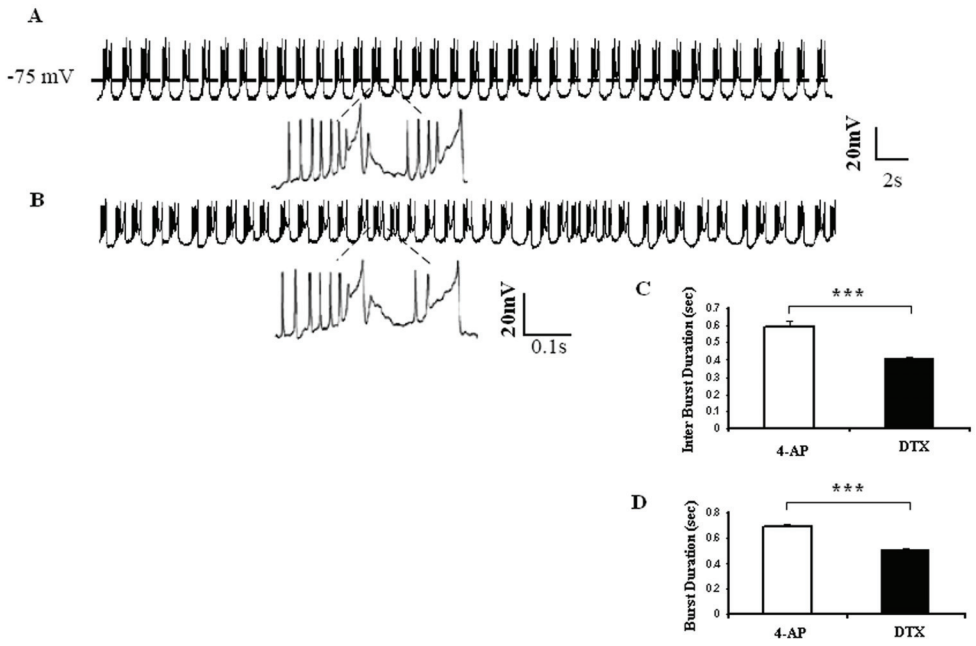

Fig. 2. Rhythmic burst activity was recorded after 4-AP and DTX superfusion. (**A**) 4-AP resulted in a rhythmic discharge with a burst pattern. Inset shows calcium spike at the end of each sodium spike burst on expanded time scale. (**B**) The effect of DTX on the spontaneous firing behavior of Purkinje neurons. In neurons pretreated with 4-AP, the interburst interval (**C**) and the burst duration (**D**) were both significantly decreased in the presence of DTX ($p<0.001$, n=42).

perfusion inlet tube to different reservoirs. 4-AP and α-dendrotoxin (DTX) were obtained from Sigma (Germany), kynurenic acid from Fluka (Germany) and picrotoxin from Tocris (UK). All data are expressed as means ± S.E.M. Student's *t*-test was used for statistical evaluation. Differences were considered significant at a level of $p<0.05$.

Results

The resting membrane potential of PCs which was estimated during the absence of a hyperpolarizing DC current was –63.4±0.9 mV ($n=66$). PCs fired consecutive active bursts interrupted by quiescent periods (Fig. 1A).

After application of a hyperpolarizing pulse, a prominent rebound depolarization (RD) was evoked (Figs 1B and 2A). Under control conditions the presence of RD was not accompanied by an associated burst of action potential. In response to a hyperpolarizing current pulse voltage-dependent 'sag' was apparent, which was clearer and more evident at stronger hyperpolarizing current injections. The voltage 'sag' was calculated by the ratio of the inward peak voltage and end voltage elicited in response to current injections (500 ms; –0.1 to –1 nA, sag ratio at –0.8 nA was 0.89 in the control condition; Fig. 1B).

In response to external 4-AP (2 mM), burst firing was initiated or potentiated and PCs displayed rhythmic Na^+-Ca^{2+} spike burst discharges from the resting membrane potential, with the burst and interburst durations being 0.69± 0.03 s ($n=42$) and 0.59±0.03 s ($n=42$), respectively (Figs 2C and D). For Na^+-Ca^{2+} spike bursts, burst duration refers to the time from the onset of the first Na^+ spike evoked by the underlying membrane depolarization to the time on the falling phase of the terminal Ca^{2+} spike corresponding to the same voltage level as the initial Na^+ spike inflection potential. A close examination of voltage trajectories underlying the 4-AP-induced rhythmic discharges in Purkinje cells revealed periodic hyperpolarizations, which halted tonic spikes and allowed the fire-pause cycle to occur continuously (Fig. 2A).

Addition of 4-AP (2 mM) resulted in delayed repolarization of the action potential and significantly broadened spikes to 123±7 % ($n=9$, $p<0.01$) of the control (Fig. 3B). The I_A channel blocker also caused a substantial increase in the number of spikes and the spike amplitude of PCs to 292±75 % ($n=15$, $p<0.05$) and 229±32 % ($n=15$, $p<0.001$) of the control, respectively (Fig. 3B). 4-AP significantly augmented the amplitude of post-pulse AHP (PPAHP) to 152±12 of the control ($n=15$, $p<0.001$, Fig. 3B). The amplitude of PPAHP was measured after the exposure to 4-AP at its peak following to the end of the pulse. This value was subtracted from the membrane potential immediately prior to the onset of

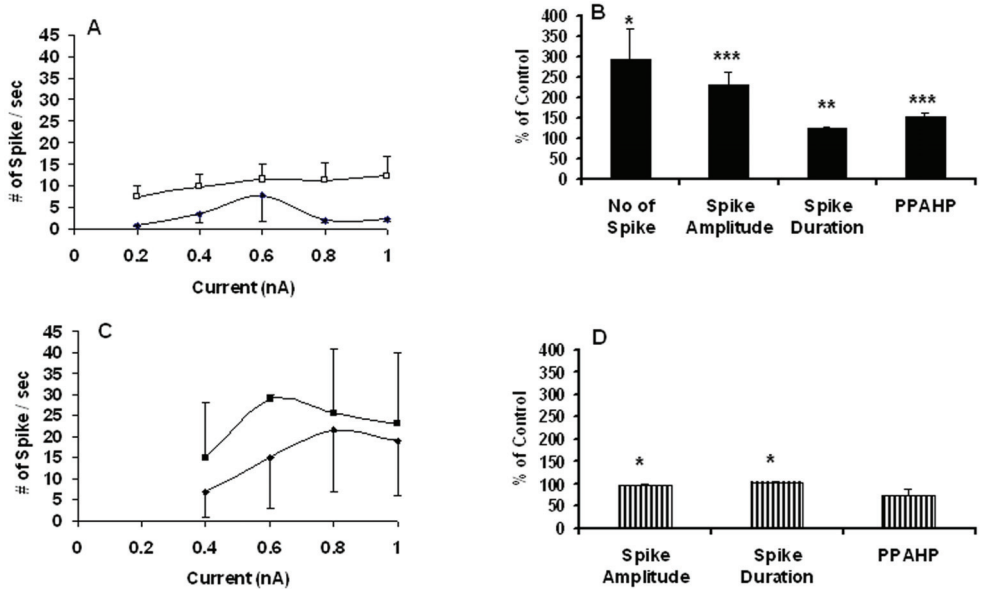

Fig. 3. Actions of 4-AP (2 mM) and DTX (200 nM) on action potential characteristics of Purkinje neurons. Purkinje neurons in the presence of 4-AP discharged more action potential than control neurons (**A**). It also had significant effects on number of spike, spike amplitude, spike duration and PPAHP (**B**). DTX increased the spike rate (**C**) and significantly reduced the spike amplitude and increased spike duration (**D**) *P<0.05, ** P<0.01, ***P<0.001.

the pulse. Repetitive firing in response to depolarizing current injection (500 ms) was evaluated by measuring the number of spikes versus the amplitude of injected current (0.2-1.0 nA). The firing response was increased after 4-AP exposure (Fig. 3A) so that in response to the injection of 0.4 nA depolarizing current pulse of 600 ms, the number of action potentials increased to 289 % of the controls (from 3.4±1.9 in control to 9.8±2.9 action potentials per second after application of 4-AP).

α-DTX, which blocks several Kv1 channels including Kv1.1, 1.2 and 1.6 subunits (Chandy and Gutman 1995, Coetzee *et al.* 1999, Brew and Forsythe 1995), increased the repetitive firing capabilities of the cells (Fig. 2B). α-DTX (200 nM) reduced the membrane accommodation and neurons became capable of firing considerably more spikes in response to the same current injection (Fig. 4). It also suppressed a fast AHP, but left the slow component of AHP intact (Fig. 4E). In the presence of DTX (200 nM), hyperpolarizing current pulses (0.1-1.0 nA) revealed a prominent inward rectification characterized by a 'sag' (sag ratio at –0.8 nA was 0.92) followed by a depolarizing rebound that triggered a burst of action potentials. Figure 1C shows a typical example of a neuron in the presence of α-DTX, that exhibited rebound firing and clear 'sag' in response to a hyperpolarizing current (–0.8 nA). α-DTX was found both to broaden spikes and to prevent broadening during repetitive firing (Geiger and Jonas 2000). We therefore examined the effects of α-DTX on spike broadening. In Purkinje cell neurons, when α-DTX (200 nM) was applied in the presence of 4-AP, it caused a significant increase in spike duration to 105.4±2.2 % of the control (n=12, p<0.05, Fig. 3D). However, DTX alone did not change the action potential duration. This result indicates that the α-DTX-sensitive current is not a major contributor to action potential repolarization in these neurons. Furthermore, exposure to α-DTX (200 nM) led to a non-significant change in the amplitude of action potential to 96.8±1.5 % of the control (n= 9, Fig. 3D). Blockade of Kv1 channel currents with DTX reduced the burst and interburst durations significantly (p<0.001) compared to those evoked in the presence of 4-AP (Figs 2C and 2D). The firing responses to the depolarizing steps (0.1-1.0 nA, 500 ms) were non-significantly increased when DTX (200 nM) was applied following exposure of PCs to 4-AP (Fig. 3C).

Discussion

Regulation of voltage- and Ca^{2+}-dependent K^+ channels function has long been recognized as a major mechanism to achieve dynamic regulation of intrinsic neuronal excitability in a number of mammalian neurons. Neurons express a wide variety of Kv channels that can contribute to diverse aspects of neuronal signaling, depending on the functional characteristics, abundance and distribution of the channel subtypes (Song 2002). Previous studies (Womack and Khodakhah 2002a,b,

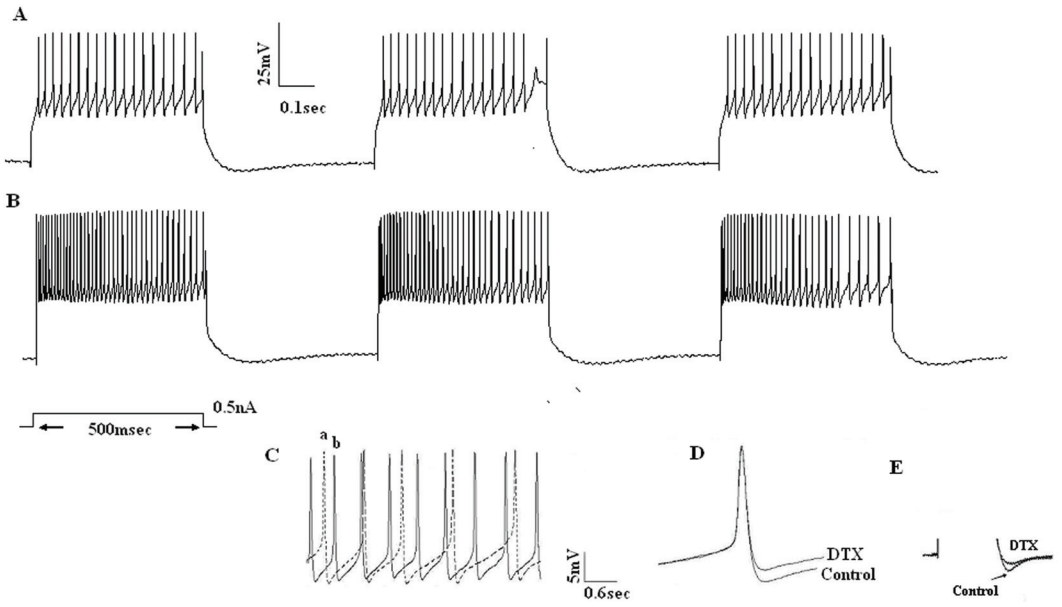

Fig. 4. Effect of DTX on evoked firing response of Purkinje neurons. Evoked response of Purkinje neuron in control (**A**) and in the presence of 200 nM DTX (**B**). (**C**) The traces are displayed expanded and superimposed under the control conditions (**A**) and after DTX application (**B**). (**D**) action potentials have been superimposed (before and after applying DTX) to show the blocking effect of DTX on the AHP. (**E**) superimposed PPAHP in response to 500 ms depolarizing current injection before and after DTX application.

2003, McKay and Turner 2004) indicated that K^+ channels regulate the action potential firing properties of PCs. Furthermore, the findings of this study have demonstrated that repetitive firing properties of PCs in rats are powerfully shaped by K^+ currents closely similar to Kv1, including A (4-AP-sensitive) and D (α-DTX-sensitive) currents and Ca^{2+}-activated K^+ (IBTX- and apamin-sensitive) channel currents. During 4-AP application, the action potential response rate and amplitude were augmented and the duration of spikes was increased. It also increased the PPAHP amplitude. 4-AP produces an increase in spike amplitude in some preparations by reducing shunting of inward conductances. In those preparations where this occurred, the activation of other voltage-dependent outward conductances, and hence AHP and PPAHP, may be increased. The spike broadening and increase in the repolarization time caused by 4-AP suggests that 4-AP-sensitive currents play a major role in spike repolarization. Previous studies have addressed the effects of 4-AP application on spike output in Purkinje cells (Llinas and Sugimori 1980, Midtgaard *et al.* 1993, Etzion and Grossman 1998, Seo *et al.* 1999, Sacco and Tempia 2002, Cavelier *et al.* 2003). For instance, application of 2 mM 4-AP has been shown to affect Ca^{2+} spikes and the oscillatory frequency of Purkinje cells (Midtgaard *et al.* 1993, Etzion and Grossman 1998, Seo *et al.* 1999). There is a controversy regarding the contribution of D currents to the firing patterns of PCs. It has been reported (Southan and Robertson 2000) that DTX-sensitive K^+ channels are present in basket cell terminals which play an important role in modulating cerebellar inhibitory synaptic transmission. DTX also increased excitability in the medial nucleus of the trapezoid body (MNTB) neurons (Brew *et al.* 2003). Different roles have been proposed for the DTX-sensitive K^+ currents reported in some neurons that fire repetitively in response to current steps. For example, a rapidly activating, slowly inactivating low threshold K^+ current in hippocampal CA1 pyramidal neurons delayed the onset of spiking during current steps; it was pointed out that its slow inactivation and slow recovery from inactivation could allow synaptic inputs to be integrated throughout time windows lasting hundreds of milliseconds (Storm 1988).

The DTX sensitivity of similar currents was confirmed later in hippocampal neurons (Wu and Barish 1992, Golding *et al.* 1999), cortical neurons (Foehring and Surmeier 1993) and neostriatal neurons, in which this current also caused spiking delays (Nisenbaum *et al.* 1996). The block of D current has generally led to only slight increases in action potential duration. For example, DTX only slightly increased AP duration in rat or mouse MNTB neurons, presumably because action potential repolarization was dominated by the much larger TEA-sensitive HVA conductance (Brew and Forsythe 1995, Wang *et al.* 1998). Consistent with this, α-DTX had only non-significant small effects on action potential duration

in PCs. There were also small or no effects of DTX on action potential duration in many other neurons and axons (Stansfeld and Feltz 1988, Nisenbaum *et al.* 1996, Rathouz and Trussell 1998, Golding *et al.* 1999).

In the present study, DTX produced a profound change in firing behavior. Modulatory effect of DTX on the neuronal excitability has been shown. Cortical pyramidal neurons express an α-DTX-sensitive current with profound effects on repetitive discharge near the rheobase (Bekkers and Delaney 2001). PCs exhibited a prominent rebound depolarization (RD), which was associated with a Na^+ spike burst when exposed to 200 nM DTX. There is a strong modulation of the amplitude and duration of the RD by apamin, but there is no evidence regarding the effect of D-type channel blocker. Here we have shown that the application of DTX resulted in a robust enhancement of the RD and caused Purkinje cells to display spontaneous bursts. This suggests that the D current modulates the RD and it can play an important role in defining the spiking pattern of PCs.

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