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Research Report

Cortical GABAergic neurons and cerebellar Purkinje cells respond to ischemia-pathogenic factors differently

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ARTICLE INFO

Article history:
Accepted 14 January 2011
Available online 22 January 2011

Keywords:
Ischemia
Acidosis
Intracellular Ca^{2+}
GABAergic neuron
Purkinje cells
Whole-cell recording and action potential

ABSTRACT

GABAergic neurons in the central nervous system are vulnerable to hazard situations, such as ischemia and toxic substances, under which their dysfunction results in neuronal excitotoxicity and subsequently cell death. How ischemia-related pathogenic factors influence the functions of different GABAergic neurons remains to be documented. We investigated this issue at cortical GABAergic neurons and cerebellar Purkinje cells in brain slices by whole-cell recordings. Our results demonstrate that ischemia, cellular Ca^{2+}-overload and acidosis lower the spike capacity of cortical GABAergic neurons, but elevate that of cerebellar Purkinje cells. These changes of spike encoding at two types of GABAergic cells are associated with the different effects of three factors on spike refractory periods and threshold potentials, which are mediated by voltage-gated sodium channels. Mechanisms underlying such differences are discussed.

1. Introduction

Action potentials are one type of essential brain codes to encode the messages of controlling well-organized behaviors and cognition (Fricker and Miles, 2001; Kandel et al., 2000; Klyachko and Stevens, 2006; Rieke et al., 1998; Shepherd, 2004; Wang et al., 2008). In terms of neural pathophysiology for brain dysfunction during the early stage of ischemia, it has been reported that the deterioration of neuronal excitability is involved (Hamann et al., 2005; Huang et al., 2010; Wang, 2003; Zhao et al., 2008), and that cortical GABAergic neurons and cerebellar Purkinje neurons are vulnerable to ischemia (Huang et al., 2010; Shuaib and Breker-Klassen, 1997; Wang, 2003; Welsh et al., 2002; Zhao et al., 2008).

The mechanisms underlying neuronal dysfunction in the early phase of ischemia include the overloads of intracellular Ca^{2+} (Aronowski et al., 1992; Block, 1999; Lipton, 1999; Mitani et al., 1995; Morioka et al., 1992; Schwartz-Bloom and Sah, 2001; White et al., 2000) and proton (Huang et al., 2010; Simon and Xiong, 2006). In addition, Ca^{2+} signals are differently distributed in cortical GABAergic neurons and cerebellar Purkinje cells (Qi et al., 2009). Do these ischemia-related factors influence the functions of cortical GABAergic cells and cerebellar Purkinje cells differently? Our studies by whole-cell recording in brain slices reveal that ischemia, cellular Ca^{2+}-overload and acidosis impair spike encoding at two types of GABAergic neurons differently.

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doi:10.1016/j.brainres.2011.01.046

2. Results

2.1. *Ischemia regulates spike encoding at cortical and cerebellar GABAergic neurons differently*

Sequential spikes at cortical GABAergic neurons and cerebellar Purkinje cells were recorded by whole-cell current-clamp. Inter-spike intervals (ISI) were measured to assess spike capacity (Chen et al., 2006a). Fig. 1 illustrates the changes of sequential spikes at these GABAergic cells during ischemia.

In cortical GABAergic neurons, ischemia reduces spike capacity (Fig. 1A). ISI values from spikes 1–2 up to 4–5 are 7.5±0.36, 8.0±0.35, 9.38±0.36 and 10.5±0.4 ms under the control (open symbols in Fig. 1B; $n=21$); and these values are 11.0±0.8, 13.3±1.4, 15.6±1.5 and 17.6±1.4 ms during ischemia (filled ones, $n=21$). ISI values for the corresponding spikes under two conditions are statistically different ($p<0.01$). Ischemia attenuates spike capacity at cortical GABAergic neurons.

On the other hand, ischemia increases spike capacity at cerebellar Purkinje cells (Fig. 1C). ISI values from spikes 1–2 to 4–5 are 9.5±0.76, 12.9±1.0, 13.8±0.9 and 14.8±0.9 ms under the control (open symbols in Fig. 1D; $n=23$); and these values are 7.4±0.8, 10.2±1.0, 11.6±0.8 and 12.0±0.8 ms during ischemia (filled ones, $n=23$). ISI values for the corresponding spikes under two conditions are statistically different ($p<0.01$). Ischemia increases spike capacity at cerebellar Purkinje cells.

2.2. *Intracellular Ca^2 regulates spiking at cortical and cerebellar GABAergic neurons differently*

Intracellular Ca^{2+} was elevated by infusing adenophostin-A into these neurons through the recording pipettes (Chen et al., 2008). Fig. 2 shows the changes of sequential spikes at these GABAergic cells during intracellular Ca^{2+} overload.

In cortical GABAergic neurons, high intracellular Ca^{2+} reduces spike capacity (Fig. 2A). ISI values from spikes 1–2 up to 4–5 are 7.5±0.36, 8.0±0.35, 9.38±0.36 and 10.5±0.4 ms under the control (open symbols in Fig. 2B, $n=21$); and these values are 8.9±0.2, 9.9±0.33, 12.0±0.6 and 14.2±0.9 ms after elevating intracellular Ca^{2+} (filled ones, $n=19$). ISI values for the corresponding spikes under these two conditions are statistically different ($p<0.01$). Intracellular Ca^{2+}-overload lowers spike capacity at cortical GABAergic neurons.

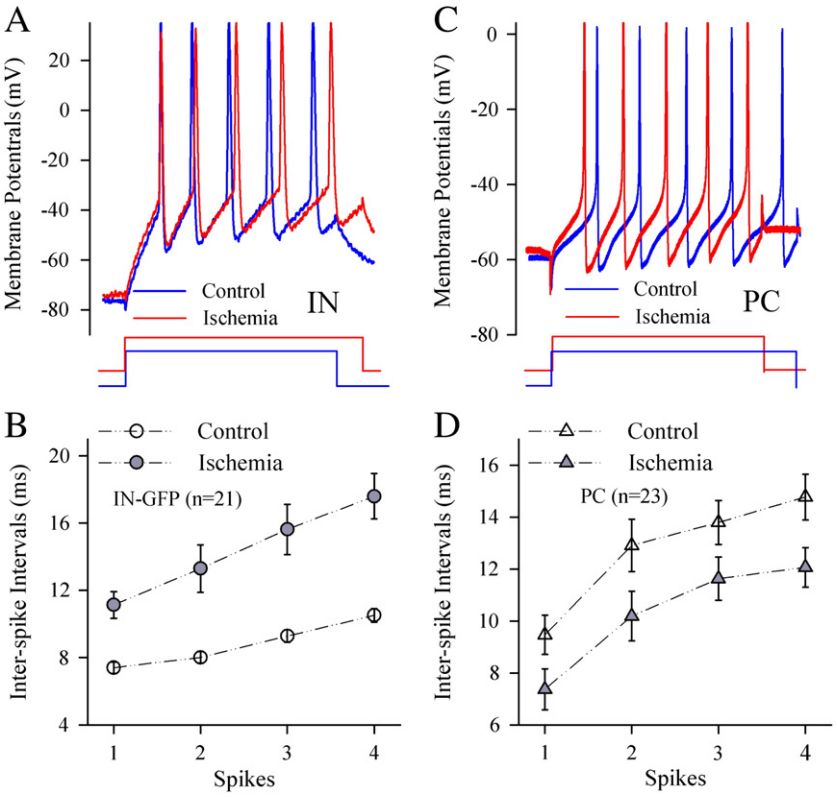

Fig. 1 – Ischemia attenuates spike capacity at cortical GABAergic neurons and enhances spike capacity at cerebellar Purkinje cells in brain slices. A) **Sequential spikes evoked by depolarization pulse 3 min after reducing perfusion rate (red trace) vs. control (blue trace) at cortical GABAergic neurons.** B) **shows inter-spike intervals (ISI) of sequential spikes under the control (open symbols) and ischemia (filled symbols, $p<0.01$, $n=21$) at cortical GABAergic neurons.** C) **Sequential spikes evoked by depolarization pulse 3 min after reducing perfusion rate (red trace) vs. control (blue trace) at cerebellar Purkinje cells.** D) **shows inter-spike intervals (ISI) of sequential spikes under the control (open symbols) and ischemia (filled symbols, $p<0.01$, $n=23$) at cerebellar Purkinje cells.**