ELSEVIER

European Journal of Pharmacology 407 (2000) 237–244

ejp

www.elsevier.nl/locate/ejphar

Adenosine action on interneurons and synaptic transmission onto interneurons in rat hippocampus in vitro

He Li [1], James L. Henry *

Departments of Psychiatry and Physiology, 3655 Drummond St., McGill University, Montreal, QC Canada H3G 1Y6

Received 15 June 2000; received in revised form 21 August 2000; accepted 24 August 2000

Abstract

To investigate the action of adenosine on interneurons as well as on excitatory synaptic transmission onto interneurons in the hippocampus, intracellular recordings were made from electrophysiologically identified interneurons in the CA1 region of the hippocampal slice in vitro. The effects of adenosine and the preferential adenosine A_1 receptor agonist, chloroadenosine, were examined. Application of 50 μM adenosine and 20 μM chloroadenosine to the bath produced a hyperpolarization of 5.6 ± 1.6 ($n = 5$) and 6.1 ± 1.4 mV ($n = 6$), respectively, as well as a decrease in membrane input resistance of $18.1 \pm 3.5\%$ ($n = 5$) and $18.5 \pm 1.4\%$ ($n = 6$), respectively. Adenosine depressed the postsynaptic potentials (PSPs) elicited in the interneurons by stimulation of Schaffer collateral fibers by $73 \pm 6.8\%$ ($n = 5$). The amplitude and the duration of the afterhyperpolarization which followed the spike of the action potential were attenuated by $48 \pm 6.9\%$ and $31 \pm 8.6\%$, respectively ($n = 5$). Chloroadenosine depressed the evoked PSPs in these interneurons by $61.2 \pm 2.7\%$ ($n = 6$) and depressed the duration and the amplitude of the afterhyperpolarization by $85.2 \pm 4.5\%$ and by $72.6 \pm 4.8\%$, respectively ($n = 6$). The data show that adenosine and chloroadenosine directly inhibit hippocampal CA1 interneurons by blocking the synaptic input, by hyperpolarizing the membrane potential and by depressing the afterhyperpolarization following individual action potential spikes. It is proposed that adenosine A_1 receptors are present at pre- and/or postsynaptic sites of interneuron synapses in the hippocampal CA1 region. The present findings demonstrate that adenosine A_1 receptor activation in CA1 interneurons is able to modulate the excitatory synaptic input to, and excitability of, these neurons. Thus, as adenosine is released during ischemia and epilepsy, adenosine may protect both interneurons and pyramidal cells from glutamate excitotoxicity through activation of adenosine A_1 receptors on these neurons in the hippocampus.

Keywords: Adenosine; Chloroadenosine; Interneuron; Hippocampus; Afterhyperpolarization

1. Introduction

Although the direct effects of adenosine on hippocampal pyramidal cell excitability and on excitatory synaptic transmission onto pyramidal cells appear to be clearly demonstrated, its effects on interneurons are not well established. Effects of adenosine on excitatory input onto hippocampal interneurons have been demonstrated only under conditions of anoxia (Doherty and Dingledine, 1997; Khazipov et al., 1995). In fact, it has been reported that adenosine fails to depress monosynaptic IPSPs (inhibitory postsynaptic potentials) in CA1 pyramidal cells (Yoon and Rothman, 1991; Thompson et al., 1992; Kamiya, 1991) and has no effect on γ-aminobutyric acid (GABA) release in the hippocampus (Burke and Nadler, 1988), suggesting there may be lack of adenosine receptors in the region of inhibitory terminals from interneurons to the pyramidal neurons in the hippocampal CA1 region. Recently, however, adenosine A_1 receptor expression has been demonstrated on some interneurons in the CA1 area using immunohistochemical detection (Rivkees et al., 1995) and in striatal interneurons using single-cell reverse transcription-polymerase chain reaction (Song et al., 2000). Moreover, adenosine A_{2A} receptor agonist CGS 21680 is able to enhance the evoked GABA release from hippocampal nerve terminals indicating adenosine may modulate the

* Corresponding author. Tel.: +1-514-398-6003; fax: +1-514-398-4370.

E-mail addresses: hli@usuhs.mil (H. Li), jhenry@med.mcgill.ca (J.L. Henry).

[1] Present address: Department of Psychiatry, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Road, Bethesda MD 20814-4799.

0014-2999/00/$ - see front matter
PII: S0014-2999(00)00661-0

hippocampal functions by acting on adenosine receptor in the interneurons as well. (Cunha and Ribeiro, 2000). However, direct electophysiological evidence of adenosine action on interneuron and interneuronal circuitry has not yet been shown in hippocampus.

Adenosine effects on interneurons are not necessarily of secondary importance to overall regulation of function in the hippocampus. It has been demonstrated that one interneuron could form approximately 25,000 synapse within the hippocampus (Sik et al., 1994). Thus, despite the fact that interneurons comprise less than 10% of the neuronal population of the hippocampus (Olbrich and Braak, 1985; Buhl et al., 1994), these interneurons may have powerful modulatory effects on pyramidal cells. Interneurons inhibit pyramidal cells by the release of GABA (Andersen et al., 1963; Alger and Nicoll, 1982). Thus, any inhibition of these inhibitory interneurons may lead to increased excitability of pyramidal cells. In fact, blockade of $GABA_A$ receptors has been shown to lead to epileptiform activity in pyramidal cells(Prince, 1985), supporting the idea that these interneurons may provide an important homeostatic control of synaptic inputs to pyramidal cells.

In this paper, we report recording intracellularly from electrophysiologically identified interneurons in the CA1 region of the rat hippocampus in vitro to examine the effects of adenosine on these neurons as well as on synaptic inputs to these neurons. Based on these observations from physiological and pharmacological analyses we confirm that the inhibitory effects of adenosine on the CA1 interneurons are mediated by activation of adenosine receptors on postsynaptic and presynaptic sites of these interneurons.

2. Materials and methods

Guidelines in The Care and Use of Experimental Animals by the Canadian Council on Animal Care (vols. I and II) were strictly followed and all experiments were approved by the McGill University Animal Care Committee.

2.1. Preparation of slices

Slices of hippocampus were prepared and perfused as previously described (Li and Henry, 1992). To outline the methods briefly, brains were removed from adult male Sprague–Dawley rats (125–225 g) after anaesthesia with halothane and decapitation with a guillotine. The hippocampus was dissected in cold oxygenated (95% O_2, 5% CO_2) artificial cerebrospinal fluid (CSF; in mM: NaCl, 124; KCl, 3; $MgCl_2$, 2; $CaCl_2$, 2; NaH_2PO_4, 1.25, $NaHCO_3$, 26; glucose, 10; pH 7.4) and transverse slices 450-μm-thick were cut using a McIlwain tissue chopper. In each case, slices were fixed on a nylon mesh in a perfusion interface chamber (600 μl) which was perfused at a rate of 1 ml/min with artificial CSF at 30°C, aerated with 95% O_2 and 5% CO_2. To allow stabilization, the slices were maintained in the chamber for >1 h before electrical recording was attempted. Stable intracellular recording was taken for >20 min before any drug was applied.

2.2. Recording and stimulation

The microelectrode for intracellular recording was drawn from WPI 1.2 mm OD, filamented glass tubing and was filled with 3 M KCl. The electrode was placed in the CA1 region under visual guidance using a Zeiss/Jena Opmi 211 stereomicroscope. An Axoclamp-2A bridge amplifier (Axon Instruments) was used for voltage recordings and for current injection through the recording pipette. Bridge balance was monitored continuously. The output signal was filtered at 10 kHz. The amplifier was connected in turn to a Tektronix 5111 oscilloscope and through a

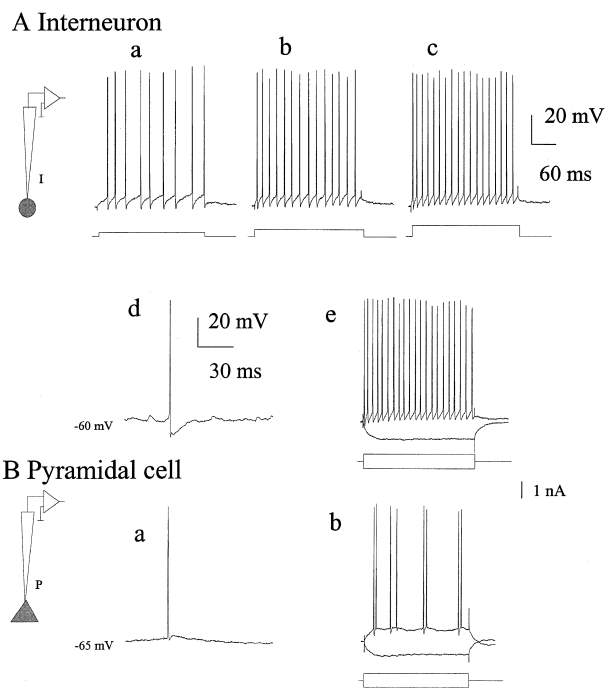

Fig. 1. Comparison of the properties of an interneuron (A) and of a pyramidal cell (B) in the CA1 region of the hippocampus. (Aa), (Ab), (Ac) and (Ae) show the sustained high frequency of firing of the interneuron in response to maintained intracellular current injection of 0.2, 0.3, 0.4 and 0.5 nA, respectively (calibration indicated to the lower right of (Ae)). The spike train was non-decrementing. Note the lack of membrane depolarization in response to the injected positive current pulses. (Ad) shows a spontaneous action potential in this interneuron. This action potential was followed by a prominent afterhyperpolarization lasting about 30 ms. In the pyramidal cell in (Ba), a depolarizing afterpotential followed a spontaneous action potential. Intracellular current injection of 0.5 nA produced a few initial action potentials followed by a period of accommodation (Bb). Hyperpolarizing current pulses induced similar downward deflections in both the interneuron (Ae) and the pyramidal cell (Bb). Calibration in (Aa)–(Ac) applies to (Ae) and (Bb) and the calibration in (Ad) applies to (Ba).

Data Translation DT2821 analogue-to-digital board to an IBM 386 personal computer for data sampling and for analysis using J. Dempster's software and software developed in our laboratory. Data were stored on magnetic tape after being fed through a pulse code modulator (Instrutech VR-100) to a video cassette recorder. The translating frequency was set at 18 kHz. Membrane potential was plotted continuously on a chart recorder (Gould 2200). Quantitative data are given as mean ± S.E.M. Statistical significance was analyzed by a paired *t*-test.

Stimulation was with bipolar NiCr twisted wire electrodes at 0.05–0.1 Hz and an intensity set to evoke responses. To activate Schaffer collateral afferents and evoke postsynaptic potentials (PSPs) onto the interneurons (Davies et al., 1990; Thompson et al., 1992) the stimulation electrode was positioned at the border of CA1 and CA2. During drug administration, the amplitude of the PSP and input resistance as well as amplitude and duration of afterhyperpolarization following the action potential were measured at the time that effect of adenosine and chloroadenosine were maximum. Otherwise, the membrane potentials were held at the initial level before drug administration. The measurements during control and after drug administration were averages of five consecutive

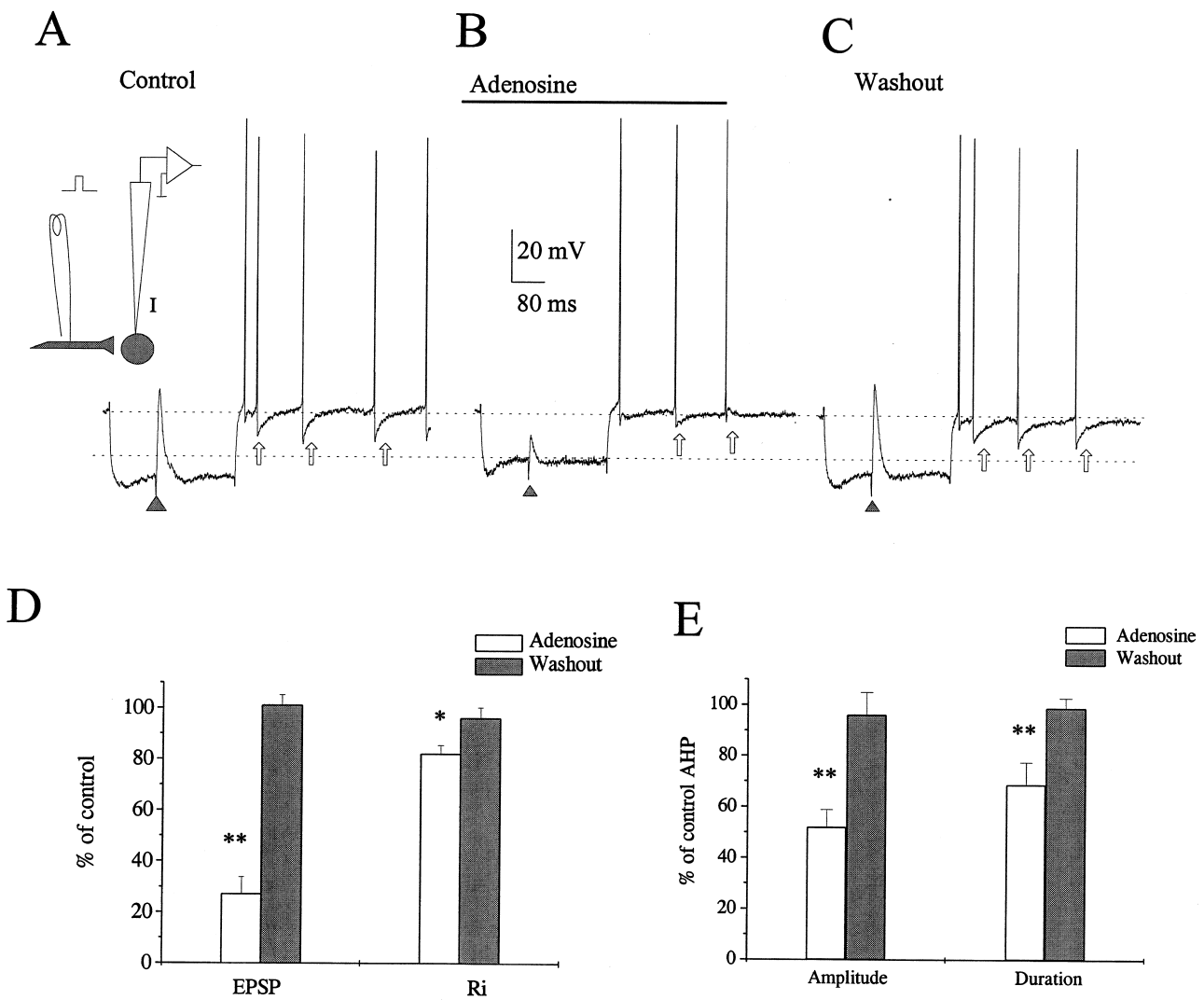

Fig. 2. Adenosine (50 μM) depresses the PSPs (indicated by filled triangle) elicited in a CA1 interneuron by stimulation of Schaffer collateral afferents, and attenuates both the amplitude and the duration of the afterhyperpolarization following the spikes (indicated by open arrows), as well as input resistance; the downward deflections were due to intracellular injections of hyperpolarizing current pulses. (A) Control evoked PSPs and spontaneous action potentials before administration of adenosine. The PSP was evoked during the injection of a hyperpolarizing current pulse to avoid generation of action potentials. (B) Record taken during the application of 50 μM adenosine; the membrane potential was held at the initial potential. During the application of adenosine the membrane was hyperpolarized, the input resistance was decreased, the evoked PSP was depressed and the amplitude and duration of the afterhyperpolarization were depressed. (C) Full recovery of these parameters after washout of adenosine. The initial resting membrane potential was −60 mV. The recording electrode was filled with 3 M KCl. (D) The cumulative data illustrate that both PSPs and input resistance (Ri) were depressed (mean ± S.E.; $n = 5$). (E) The cumulative data illustrate that both the amplitude and the duration of the afterhyperpolarization were attenuated ($n = 5$). Full recovery was seen in all cases. $^{*} = p < 0.05$ and $^{**} = p < 0.01$.

evoked PSP and afterhyperpolarization following the action potentials.

2.3. Drugs

Adenosine (Sigma, Oakville, Ontario) and 2-chloroadenosine (Sigma) were applied by addition to the perfusion fluid at known concentrations. Chloroadenosine was chosen because it acts preferentially on adenosine A_1 receptors and it is considerably more soluble in water than more selective adenosine A_1 receptor agonists (Bruns et al., 1980; Daly, 1982). Drugs were prepared as 10-fold concentrated aqueous aliquots and stored frozen.

3. Results

3.1. Identification of interneurons *vs.* pyramidal cells

3.1.1. Interneurons

Interneurons were identified electrophysiologically by their characteristic properties distinct from pyramidal cells (see comparative data in Fig. 1): mean action potential duration measured at the base was 0.61 ± 0.06 ms; the spike of the action potential was followed by a prominent afterhyperpolarization (mean maximum amplitude of 12.4 $\pm$ 1.9 mV; mean duration of 26 ± 2.7 ms); a depolarizing current pulse produced a sustained high frequency of firing (Fig. 1(A)). Thus, all of the interneurons included in this study were typical basket cells which contact primarily the somata of pyramidal cells (Buhl et al., 1994; Nicoll, 1994). The membrane properties of the 11 interneurons were: mean resting membrane potential of -61.2 ± 2.1 mV and mean input resistance of 33.7 ± 3.6 MΩ.

3.1.2. Pyramidal cells

Stable intracellular recording were taken from 35 pyramidal cells in the pyramidal cell layer of the CA1 region (Fig. 1(B). The mean resting membrane potential of the cells included in this study, measured upon withdrawal of the electrode, was -66.2 ± 2.8 mV ($\pm$S.E.M.). The mean input resistance of the cells was 37.6 ± 3.2 MΩ, determined by passing a hyperpolarizing current pulse at a duration of 200 ms across the neuronal membrane. Action potentials generated by the passage of a brief depolarizing intracellular current pulse (0.1–0.5 nA), had a mean ampli-

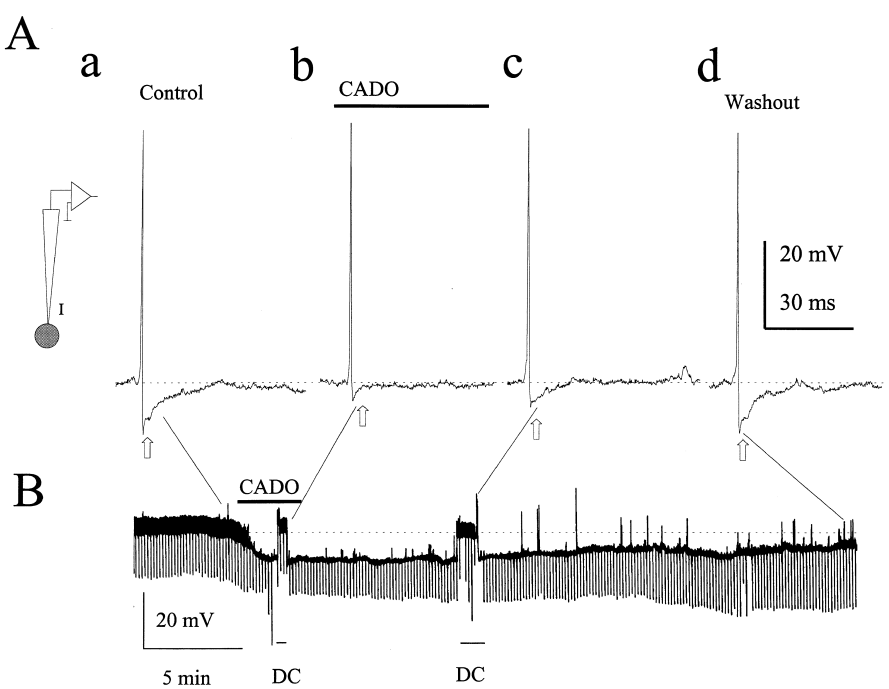

Fig. 3. Chloroadenosine (CADO) hyperpolarizes the membrane potential of an interneuron and attenuates both the amplitude and the duration of the afterhyperpolarization following a spike. (A) Spontaneous action potentials before (Aa), during (Ab) and after ((Ac) and (Ad)) administration of 20 μM chloroadenosine. Records were taken at the initial membrane potential, maintained by DC current injection. (B) Chart record of the membrane potential of the interneuron. Regularly repeated downward deflections were due to -0.4 nA intracellular current pulses. DC indicates periods of current injection to return membrane potential to the preapplication level. During the application of 20 μM chloroadenosine, the membrane was hyperpolarized and the input resistance was decreased. The amplitude and duration of the afterhyperpolarization (open arrows) were depressed. The amplitude and duration of the afterhyperpolarization before, during and after drug application were measured at the preapplication membrane potential. The resting membrane potential was -59 mV. The recording electrode was filled with 3 M KCl.

tude of 95.7 ± 3.3 mV and a mean overshoot of 26.1 ± 2.9 mV.

3.2. Effects of adenosine and chloroadenosine on CA1 interneurons and on PSPs from stimulation of Schaffer collaterals

As illustrated in Fig. 2, remote stimulation of the Schaffer collaterals elicited PSPs in CA1 interneurons (Fig. 2(Aa)–(Ac)).

Adenosine (50 μM) depressed the PSPs by 73 ± 6.8% ($n = 5$, Fig. 2(B) and (D)) and decreased input resistance by 18 ± 3.5% ($n = 5$, Fig. 2(D)). In addition, adenosine (50 μM) attenuated both the amplitude and the duration of the afterhyperpolarization following the spikes (Fig. 2, indicated by unfilled arrows) by 48 ± 6.9% and 31 ± 8.6% ($n = 5$, Fig. 2(E)), respectively. As application of 50 μM adenosine produced a hyperpolarization of 5.6 ± 1.6 mV ($n = 5$) and decreased input resistance the measurement of PSPs and the afterhyperpolarization during the application of adenosine were always taken when the membrane potential was held at the initial level by transient direct current injection. Full recovery of these parameters was observed after washout of adenosine (Fig. 2(C)).

In view of this unexpected effect of adenosine on membrane potential and input resistance as well as on the duration and amplitude of the afterhyperpolarization following an action potential, the more water soluble and preferential adenosine A_1 receptor agonist, chloroadenosine, was examined on CA1 interneurons. As illustrated in Figs. 3–5, 20 μM chloroadenosine produced a hyperpolarization of 6.1 ± 1.4 mV and decreased input resistance by 18.5 ± 1.5% ($n = 6$; Figs. 3 and 4(D)). In addition, 20 μM chloroadenosine depressed both the duration and amplitude of the afterhyperpolarization by 85.2 ± 4.6% and 72.6 ± 2.6%, respectively ($n = 6$; Figs. 3(Ab) and 4(E)). Remote stimulation of Schaffer collaterals elicited a PSP in CA1 interneurons (Figs. 2(A) and (C), 4(A) and (C), 5) and 20 μM chloroadenosine depressed this PSP by 61.4 ± 2.8% ($n = 6$; Figs. 4(B) and 5(B)). Cell input resistances and synaptic responses were assessed at different membrane potentials by applying hyperpolarizing current pulses through the recording electrode before (Fig. 5(Aa),(B),(C)), during (Fig. 5(Ab),(B),(C)) and after washout of 20 μM

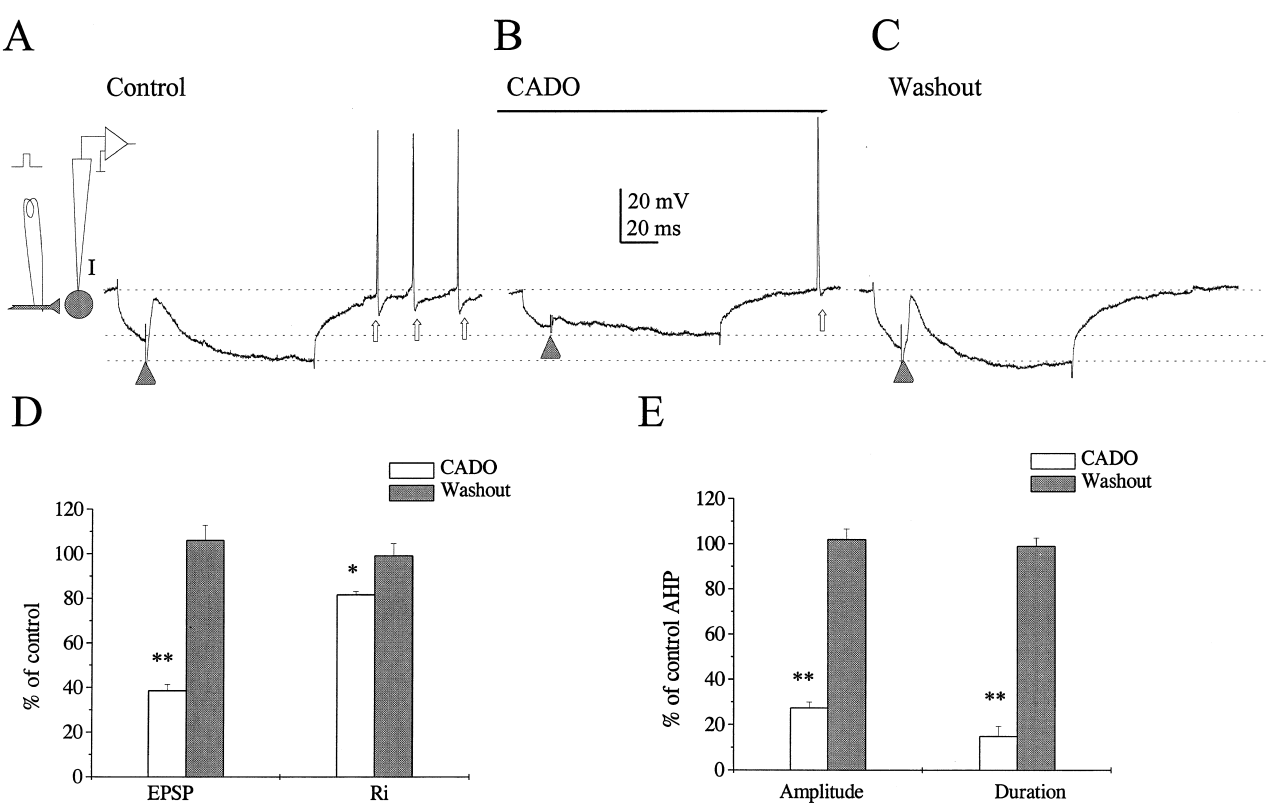

Fig. 4. Chloroadenosine (CADO) depresses the PSPs elicited in a CA1 interneuron by stimulation of Schaffer collateral afferents and attenuates both the amplitude and the duration of the afterhyperpolarization following a spike. (A) Control PSPs and action potentials evoked by stimulation before administration of chloroadenosine. (B) During the application of 20 μM chloroadenosine the membrane was hyperpolarized, the input resistance was decreased, the evoked PSPs were depressed and the amplitude and duration of the afterhyperpolarization (open arrows) were attenuated. The membrane potential was held at the initial potential. (C) Full recovery of these parameters. (D) The cumulative data illustrate that both PSPs and input resistance (Ri) were depressed (mean ± S.E.; $n = 6$). (E) The cumulative data illustrate that both the amplitude and the duration of the afterhyperpolarization were attenuated ($n = 6$). Full recovery was seen in all cases. $^{*} = p < 0.05$ and $^{**} = p < 0.01$. The recording electrode was filled with 3 M KCl.

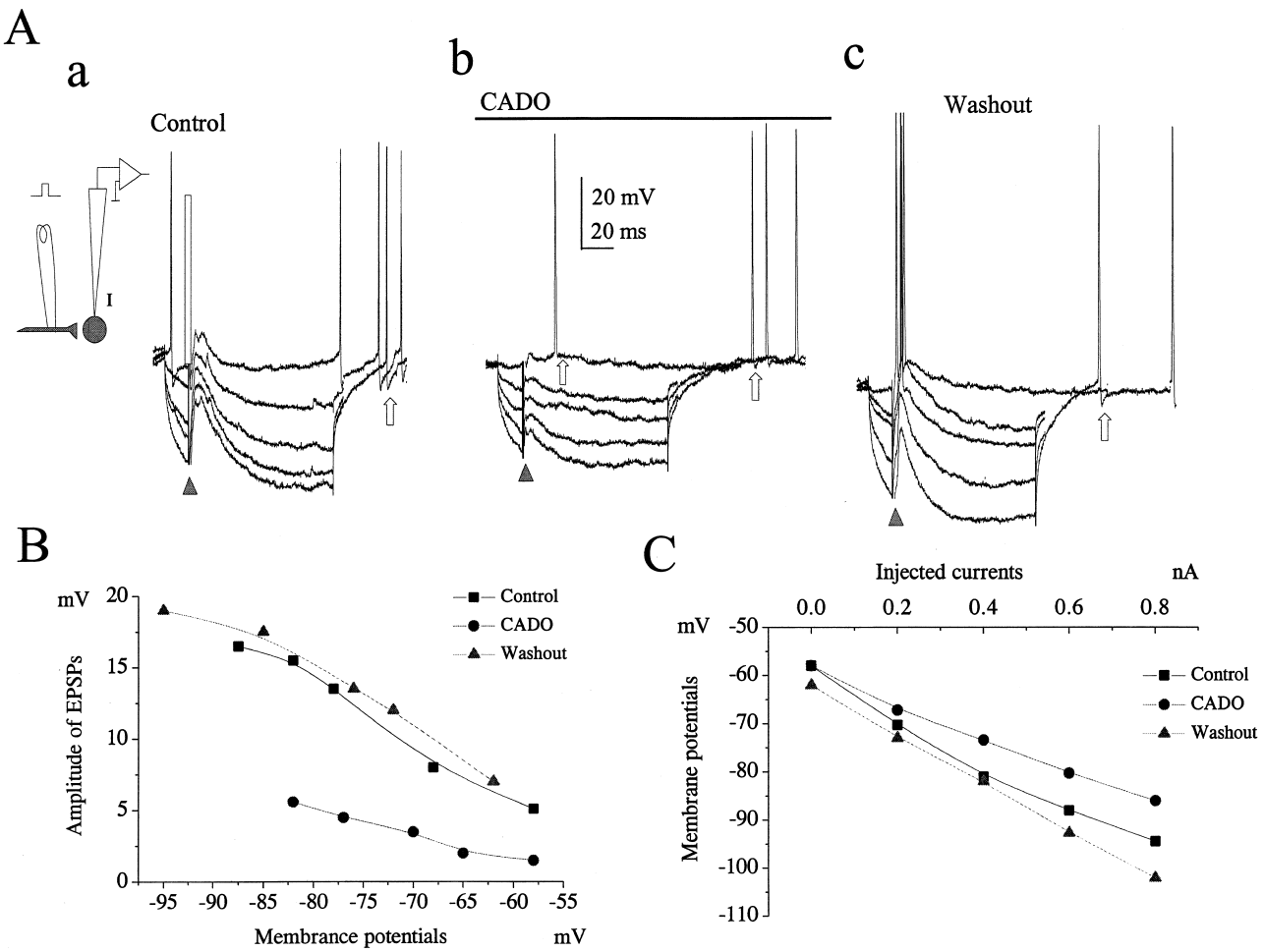

Fig. 5. At different membrane potentials, chloroadenosine (CADO) depresses the PSPs elicited in a CA1 interneuron by stimulation of Schaffer collateral afferents and decreases the input resistance. (A) Synaptic responses were recorded at the point indicated by the filled triangles. The amplitude and duration of the afterhyperpolarization (open arrows) were depressed. The change in membrane potential was induced by 120 ms duration hyperpolarizing current pulses injected through the recording electrode. (B) Relationship between the amplitude of the synaptic response and the membrane potential before (Aa), during (Ab) and after (Ac) administration of chloroadenosine. The initial resting membrane potential was −58 mV. The electrode was filled with 3 M KCl. (C) Current–voltage relationships from the data presented in (Aa), (Ab) and (Ac). Membrane potential measurements were made at the end of the depolarizing current pulses.

chloroadenosine (Fig. 5(Ac),(B),(C)). As illustrated in Fig. 5(A)–(C), there were changes in the current–voltage relationship and PSPs during the application of chloroadenosine and both input resistance and PSPs were gained full recovery after washout of chloroadenosine.

4. Discussion

4.1. Adenosine effects on membrane properties of interneurons

More than seven types of interneuron have been described in the hippocampus according to the location, electrophysiological properties, connectivity to pyramidal cells and pharmacological profile (Freund and Buzsaki, 1996). In general, three types of interneuron have been identified in the hippocampal CA1 region based on different distribution and on different morphological and electrophysiological properties (Kawaguchi and Hama, 1987, 1988; Buhl et al., 1994; Nicoll, 1994). The basket cell contacts primarily the somata of pyramidal cells (Buhl et al., 1994). The axo–axonic cell contacts primarily the axon initial segment of pyramidal cells (Buhl et al., 1994). The bistratified cell contacts primarily the apical and basal dendrites of pyramidal cells (Buhl et al., 1994). The interneurons included in this study were all basket cells in nature which are characterized as fast spiking interneurons (Schwartzkroin and Mathers, 1978) and were recorded from the stratum radiatum close to the CA1 region.

Our results demonstrate that activation of adenosine A_1 receptors hyperpolarizes the membrane and decreases the input resistance of these hippocampal interneurons. An enhancement of the afterhyperpolarization was never observed in the interneurons in our experiments. It has been demonstrated in myocytes and CA1 pyramidal cells that

adenosine induces hyperpolarization by acting on adenosine A_1 receptors to open potassium channels, including K_{ATP} channels, through a G-protein mediated mechanism (Kirsch et al., 1990; Softky and Koch, 1993; Li and Henry, 1992). However, an effect of adenosine and chloroadenosine on interneurons has not been reported previously in the hippocampal CA1 region. Our data thus provide the first electrophysiological evidence for a direct action of adenosine on hippocampal CA1 interneurons and supports the idea that adenosine can decrease interneuronal excitability and thereby may protect these neurons from excessive excitation during ischemic and anoxic attack, conditions in which the extracellular adenosine concentration is dramatically increased (Dux et al., 1990).

With regard to the decrease in the afterhyperpolarization, this may have been due to an indirect shunting effect resulting from the decrease in the input resistance of the interneurons. However, in view of the fact that there was only about an 18% decrease in the input resistance, but adenosine and chloroadenosine attenuated the amplitude of afterhyperpolarization by 48 to 85%, a shunting effect may not be able to account for all of the effect on the afterhyperpolarization.

There has been one report focusing specifically on the effects of adenosine on the afterhyperpolarization in hippocampal pyramidal cells (Haas and Greene, 1984); the data indicated an enhancement rather than a depression at doses lower than 50 μM. However, the afterhyperpolarization studied in pyramidal cells appears to have been of a different type than that studied here. Three different types of afterhyperpolarization have been demonstrated in hippocampal pyramidal cells, a fast afterhyperpolarization which lasts 2–5 ms, a medium afterhyperpolarization, generated by a burst of action potentials provoked by injection of depolarizing current, which lasts 50–100 ms and a slow afterhyperpolarization which lasts more than 1 s (Storm, 1989). The previous report studied the long-duration afterhyperpolarization and there was only an effect on the duration of the afterhyperpolarization, with no concomitant effect on the amplitude (Haas and Greene, 1984). The afterhyperpolarization of the interneurons in our experiments appears to be different from any of the three types in pyramidal cells because the average duration was 26 ms, which lies outside the ranges of the durations reported in pyramidal cells. In addition, the afterhyperpolarization in the interneurons occurred following spontaneous action potentials, while the medium and slow afterhyperpolarizations in pyramidal cells are generated by altering the excitability of these cells (Storm, 1989).

Adenosine effects on excitatory synaptic transmission in pyramidal cells in the hippocampus have been studied extensively (Greene and Haas, 1985; Thompson et al., 1992; Yoon and Rothman, 1991; Stone, 1981). The synaptic input from CA3 to CA1 interneurons is also mediated by excitatory amino acids (Lacaille, 1991; Lacaille and Schwartzkroin, 1988; Lacaille et al., 1987). Therefore, we postulated that adenosine might block the excitatory synaptic transmission to interneurons as it does the excitatory inputs to pyramidal cells in the CA1 region. Our data provide the first evidence showing that adenosine has a profound depressant effect on the PSP elicited in CA1 interneurons by stimulation of Schaffer collaterals. At a postsynaptic site, adenosine action is thought to be predominantly due to an increase in potassium conductance (Segal, 1982). Apparently whether adenosine effects on the membrane potential and afterhyperpolarization are mediated by different mechanisms needs further investigation. Depression of these excitatory inputs by adenosine may serve as a further protective mechanism for these interneurons during anoxia and ischemia (Dux et al., 1990).

In summary, our data demonstrate that adenosine receptors are located at both presynaptic and postsynaptic sites of interneurons in the CA1 region of the hippocampus. Considering the effects of adenosine on both interneurons and pyramidal cells in the hippocampus and separate distributions of adenosine receptors on the somata and terminals of interneurons, this may allow adenosine, glutamate, GABA and other neurotransmitters to affect hippocampal pyramidal cell function by regulating the excitability of inhibitory interneurons. Therefore the present findings may have potential therapeutic implications for the treatment of clinical problems such as epilepsy and the neurotoxicity which occurs with hypoxia and ischemia.

Acknowledgements

This work was supported by a Grant-in-Aid from the Quebec Heart and Stroke Foundation and by the Faculty of Graduate Studies and Research of McGill University. HL was supported by a Studentship from the Royal Victoria Hospital Research Institute and an International Canada (McGill/CIDA) Fellowship.

References

Alger, B.E., Nicoll, R.A., 1982. Feed-forward dendritic inhibition in rat hippocampal pyramidal cells studied in vitro. J. Physiol. (London) 328, 105–123.

Andersen, P., Eccles, J.C., Løyning, Y., 1963. Pathway of postsynaptic inhibition in the hippocampus. J. Neurophysiol. 27, 608–619.

Bruns, R.F., Daly, J.W., Snyder, S.H., 1980. Adenosine receptors in brain membranes: binding of N^6-cyclohexyl[^{3}H]adenosine and 1,3-diethyl-8-[^{3}H]phenylxanthine. Proc. Natl. Acad. Sci. U. S. A. 77, 5547–5551.

Buhl, E.H., Halasy, K., Somogyi, P., 1994. Diverse sources of hippocampal unitary inhibitory postsynaptic potentials and the number of synaptic release sites. Nature 368, 823–828.

Burke, S.P., Nadler, J.V., 1988. Regulation of glutamate and aspartate release from slices of the hippocampal CA1 area: effects of adenosine and baclofen. J. Neurochem. 51, 1541–1551.

Cunha, R.A., Ribeiro, J.A., 2000. Purinergic modulation of [^{3}H] GABA release from rat hippocampal nerve terminals. Neuropharmacology 39, 1156–1167.

Daly, J.W., 1982. Adenosine receptors: targets for future drugs. J. Med. Chem. 25, 197–207.

Davies, C.H., Davies, S.N., Collingridge, G.L., 1990. Paired-pulse depression of monosynaptic GABA-mediated inhibitory postsynaptic responses in rat hippocampus. J. Physiol. (London) 424, 513–531.

Doherty, J., Dingledine, R., 1997. Regulation of excitatory input to inhibitory interneurons of the dentate gyrus during hypoxia. J. Neurophysiol. 77, 393–404.

Dux, E., Fastbom, J., Ungerstedt, U., Rudolphi, K., Fredholm, B.B., 1990. Protective effect of adenosine and a novel xanthine derivative propentofylline on the cell damage after bilateral carotid occlusion in the gerbil hippocampus. Brain Res. 516, 248–256.

Freund, T.F., Buzsaki, G., 1996. Interneurons of the hippocampus. Hippocampus 6, 347–470.

Greene, R.W., Haas, H.L., 1985. Adenosine actions on CA1 pyramidal neurones in rat hippocampal slices. J. Physiol. (London) 366, 119–127.

Haas, H.L., Greene, R.W., 1984. Adenosine enhances afterhyperpolarization and accommodation in hippocampal pyramidal cells. Pflugers Arch. 402, 244–247.

Kamiya, H., 1991. Some pharmacological differences between hippocampal excitatory and inhibitory synapses in transmitter release: an in vitro study. Synapse 8, 229–235.

Kawaguchi, Y., Hama, K., 1987. Two subtypes of non-pyramidal cells in rat hippocampal formation identified by intracellular recording and HRP injection. Brain Res. 411, 190–195.

Kawaguchi, Y., Hama, K., 1988. Physiological heterogeneity of nonpyramidal cells in rat hippocampal CA1 region. Exp. Brain Res. 72, 494–502.

Khazipov, R., Congar, P., Ben-Ari, Y., 1995. Hippocampal CA1 lacunosum-moleculare interneurons: comparison of effects of anoxia on excitatory and inhibitory postsynaptic currents. J. Neurophysiol. 74, 2138–2149.

Kirsch, G.E., Codina, J., Birnbaumer, L., Brown, A.M., 1990. Coupling of ATP-sensitive K^+ channels to A_1 receptors by G proteins in rat ventricular myocytes. Am. J. Physiol. 259, H820–H826.

Lacaille, J.-C., 1991. Postsynaptic potentials mediated by excitatory and inhibitory amino acids in interneurons of stratum pyramidale of the CA1 region of rat hippocampal slices in vitro. J. Neurophysiol. 66, 1441–1454.

Lacaille, J.-C., Schwartzkroin, P.A., 1988. Stratum lacunosum-moleculare interneurons of hippocampal CA1 region. II. Intrasomatic and intradendritic recordings of local circuit synaptic interactions. J. Neurosci. 8, 1411–1424.

Lacaille, J.-C., Mueller, A.L., Kunkel, D.D., Schwartzkroin, P.A., 1987. Local circuit interactions between oriens/alveus interneurons and CA1 pyramidal cells in hippocampal slices: electrophysiology and morphology. J. Neurosci. 7, 1979–1993.

Li, H., Henry, J.L., 1992. Adenosine-induced hyperpolarization is depressed by glibenclamide in rat CA1 neurones. NeuroReport 3, 1113–1116.

Nicoll, R.A., 1994. Neuroscience. Cajal's rational psychology [news; comment]. Nature 368, 808–809.

Olbrich, H.-G., Braak, H., 1985. Ratio of pyramidal cells vs. non-pyramidal cells in sector CA1 of the human Ammon's horn. Anat. Embryol. (Berlin) 173, 105–110.

Prince, D.A., 1985. Physiological mechanisms of focal epileptogenesis. Epilepsia 26 (Supplement 1), S3–14.

Rivkees, S.A., Price, S.L., Zhou, F.C., 1995. Immunohistochemical detection of A_1 adenosine receptors in rat brain with emphasis on localization in the hippocampal formation, cerebral cortex, cerebellum and basal ganglia. Brain Res. 677, 193–203.

Schwartzkroin, P.A., Mathers, L.H., 1978. Physiological and morphological identification of a nonpyramidal hippocampal cell type. Brain Res. 157, 1–10.

Segal, M., 1982. Intracellular analysis of a postsynaptic action of adenosine in the rat hippocampus. Eur. J. Pharmacol. 79, 193–199.

Sik, A., Ylinen, A., Penttonen, M., Buzsaki, G., 1994. Inhibitory CA1-CA3-Hilar region feedback in the hippocampus. Science 265, 1722–1724.

Song, W.J., Tkatch, T., Surmeier, D.J., 2000. Adenosine receptor expression and modulation of $Ca(2+)$ channels in rat striatal cholinergic interneurons. J. Neurophysiol. 83, 322–332.

Softky, W.R., Koch, C., 1993. The highly irregular firing of cortical cells is inconsistent with temporal integration of random EPSPs. J. Neurosci. 13, 334–350.

Stone, T.W., 1981. Physiological roles for adenosine and adenosine 5′-triphosphate in the nervous system. Neuroscience 6, 523–545.

Storm, J.F., 1989. An after-hyperpolarization of medium duration in rat hippocampal pyramidal cells. J. Physiol. (London) 409, 171–190.

Thompson, S.M., Haas, H.L., Gähwiler, B.H., 1992. Comparison of the actions of adenosine at pre- and postsynaptic receptors in the rat hippocampus in vitro. J. Physiol. (London) 451, 347–363.

Yoon, K.W., Rothman, S.M., 1991. Adenosine inhibits excitatory but not inhibitory synaptic transmission in the hippocampus. J. Neurosci. 11, 1375–1380.