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ORIGINAL ARTICLE

Adenosine receptor agonists affect taurine release from mouse brain stem slices in ischemia

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Abstract The release of the inhibitory amino acid taurine is markedly enhanced under ischemic conditions in both adult and developing brain stem, together with a pronounced increase in the release of the neuromodulator adenosine. We now studied the effects of adenosine receptor agonists and antagonists on [^{3}H]taurine release in the brain stem in normoxia and ischemia, using a superfusion system. Under standard conditions, the adenosine A_1 receptor agonist N^6-cyclohexyladenosine (CHA) potentiated basal taurine release in adult mice, which response was blocked by the antagonist 8-cyclopentyl-1, 3-dipropylxanthine (DPCPX). CHA and the A_{2a} receptor agonist 2-*p*-(2-carboxyethyl)phenylamino-5′-*N*-ethylcarboxaminoadenosinehydrochloride (CGS 21680) had no effect on the release in developing mice. In ischemia, CHA depressed both basal and K^+-stimulated taurine release in developing mice in a receptor-mediated manner, blocked by DPCPX. The A_{2a} receptor agonist CGS 21680 was also inhibitory. Taurine and adenosine may thus not cooperate in developing mice to prevent ischemic neuronal damage. On the other hand, CGS 21680 enhanced taurine release in the adult brain stem in ischemia, both basal and K^+-stimulated release being affected. These effects were abolished by the antagonist 3,7-dimethyl-1-propargylxanthine (DMPX), indicating a receptor-mediated process. In this case elevated levels of taurine could be beneficial, protecting against hyperexcitation and excitotoxicity.

Keywords Taurine release · Adenosine receptors · Ischemia · Brain stem slices · Development · Mouse

Abbreviations

CGS 21680	2-*p*-(2-Carboxyethyl)phenylamino-5′-*N*-ethylcarboxaminoadenosinehydrochloride
CHA	N^6-cyclohexyladenosine
DMPX	3,7-Dimethyl-1-propargylxanthine
DPCPX	8-Cyclopentyl-1,3-dipropylxanthine
Hepes	*N*-2-hydroxyethylpiperazine-*N*′-2-ethanesulphonic acid
NBTI	*S*-(4-nitrobenzyl)-6-thioinosine
8-PT	8-Phenyltheophylline

Introduction

Adenosine as an inhibitory neuromodulator in the brain acts by means of three types of receptors, A_1, A_2, (two subtypes A_{2a} and A_{2b}), and A_3 (Cunha 2001). Presynaptically, adenosine inhibits neurotransmitter release at A_1 receptors mainly in excitatory synapses, thus reducing neuronal excitability (Latini and Pedata 2001). Postsynaptically, adenosine hyperpolarizes postsynaptic membranes through A_1 receptors by enhancing Ca^{2+}-dependent K^+ conductance (Haas and Greene 1988). Adenosine receptors are already present and functional during early brain development (Psarropoulou et al. 1990; Daval et al. 1991). The A_1 receptors are widespread and abundant in the brain, with high levels in the brain stem, while the A_{2a}

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receptors are expressed at relatively lower levels (Dixon et al. 1996; Latini et al. 1996; Fredholm et al. 2005). Activation of A_1 and A_2 receptors differentially modulates Ca^{2+} channels and glycine transmission in the brain stem (Umemiya and Berger 1994). Both receptors mediate blood pressure responses in the brain stem (Barraco and Phillis 1991; Barraco et al. 1991) and are generally involved in cardiovascular regulation (Barraco et al. 1995, 1996). Adenosine release is induced by K^+ depolarization, electrical stimulation and various agents, including ionotropic glutamate receptor agonists (Latini and Pedata 2001; Saransaari and Oja 2002). Adenosine is also released during hypoxia and ischemia (Phillis et al. 1987; Rudolphi et al. 1992; Saransaari and Oja 2003, 2004a), acting then as an endogenous neuroprotectant against cerebral ischemia and excitotoxic neuronal damage (Ongini et al. 1997; Pedata et al. 2007; Cunha 2008).

Another inhibitory compound, taurine, is also released from nervous tissue under various cell-damaging conditions (Saransaari and Oja 2000a). Taurine has been shown to be involved in several important physiological functions in the brain, serving as a trophic factor in the developing brain and maintaining the structural integrity of cell membranes (see Oja and Saransaari 2007). It regulates Ca^{2+} homeostasis and functions as an osmoregulator and an inhibitory neuromodulator (Oja and Saransaari 2007; Saransaari and Oja 2008a). Taurine is known to protect neural cells from excitotoxicity induced by excitatory amino acids (French et al. 1986; Trenkner 1990; Tang et al. 1996), to prevent harmful metabolic responses evoked by ischemia (Schurr et al. 1987) and to alleviate symptoms in epilepsy (Oja and Saransaari 2007). Moreover, taurine has recently been shown to prevent ischemia-induced apoptosis (Takatani et al. 2004; Taranukhin et al. 2008). This latter antiapoptotic function has been thought to be due to inhibition of glutamate-induced membrane depolarization (Leon et al. 2009). In the brain stem taurine has been suggested to be involved in the modulation of cardiovascular control in the ventrolateral medulla (Kubo et al. 1993; Wang et al. 2005) and neurogenic control of arterial blood pressure in the nucleus of the solitary tract (Meeley et al. 1989). Taurine is released from the locus coeruleus by various stimuli (Singewald and Philippu 1998) and there is also evidence that the taurine released therein is involved in conditioned fear (Kaehler et al. 2000). However, there is no information on the interactions of taurine and adenosine in the brain stem, although the effects of these two neuroprotective compounds could be of importance in the prevention of ischemic neuronal damage. We have recently systematically characterized the properties of taurine release in brain stem slices from both adult and developing mice (Saransaari and Oja 2006, 2007, 2008b, 2009). Now we characterized under normal and ischemic conditions the involvement of adenosine receptors in the release of preloaded [^{3}H]taurine in slices prepared from the mouse brain stem from developing (7-day old) and young adult (3-month old) mice, using a superfusion system.

Materials and methods

Materials

Developing (7-day old) and young adult (3-month old) NMRI mice of both sexes were used in the experiments. There were no gender differences in the results obtained. All procedures were in accordance with the European Community Directive for the ethical use of experimental animals and they were approved by the University Committee on Animal Experiments. All efforts were made to reduce the number of animals used and their suffering. [^{3}H]Taurine (specific radioactivity 1.15 PBq/mol) was obtained from Amersham International (Bristol, UK). The adenosine A_1 receptor agonist N^6-cyclohexyladenosine (CHA), the adenosine A_{2a} agonist 2-*p*-(2-carboxyethyl)phenylamino-5′-*N*-ethylcarboxaminoadenosinehydrochloride (CGS 21680), the A_1 receptor antagonists 8-cyclopentyl-1,3-dipropylxanthine (DPCPX), and 8-phenyltheophylline (8-PT), the A_{2a} receptor antagonist 3,7-dimethyl-1-propargylxanthine (DMPX), and the adenosine transport inhibitors *S*-(4-nitrobenzyl)-6-thioinosine (NBTI) and dipyridamole were from Sigma (St. Louis, MO, USA). The drug concentrations used are based on their biological efficacies (Klotz 2000). Other reagents were from common commercial sources.

Release experiments

Superficial slices 0.4 mm thick weighing 15–20 mg were manually prepared from the mouse brain stem with a tissue slicer of Stadie-Riggs type. The slices were immediately immersed in 5 ml of oxygenated medium and incubated with 0.01 mM [^{3}H]taurine (50 MBq/l) at 37°C for 15 min under agitation. During this period enough labeled taurine was enriched in the slices for reliable release estimation. The standard medium contained (in mmol/l) NaCl 127, KCl 5, $CaCl_2$ 0.8, $MgSO_4$ 1.3, Na_2HPO_4 1.3, *N*-2-hydroxyethylpiperazine-*N*′-2-ethanesulphonic acid (Hepes) 15, NaOH 11, and D-glucose 10 (pH 7.4). The slices were then transferred into 0.25 ml cups and superfused with the above medium (unless otherwise specified) at a rate of 0.25 ml/min for 50 min in a system in which freely floating shaken slices were kept under a continuous flow of oxygen in order to preserve their viability (Kontro and Oja 1987). The superfusion medium was pooled during the first

20 min and thereafter 2-min fractions (0.5 ml) were directly collected into small scintillation vials with a fraction collector. After superfusion the slices were weighed, homogenized in ice-cold 5% (w/v) trichloracetic acid solution, and centrifuged, and the clear supernatants used for scintillation counting. The effluent samples were subjected to the same analyses.

Superfusion conditions

Ischemic conditions were induced by modified experimental conditions: the glucose-free medium was bubbled with N_2 gas (Taylor et al. 1995) for 30 min before the experiments and then throughout superfusion.

Estimation of efflux rate constants

Desaturation curves for labeled taurine from the slices were plotted as a function of time on the basis of the radioactivities remaining in the slices after superfusion and recovered in the collected superfusate fractions (Kontro and Oja 1987). The efflux rate constants of taurine for the time intervals of 20–30 min (k_1, initial release phase) and 32–40 min (k_2, later release phase) were computed as negative slopes for the regression lines of the logarithm of radioactivity remaining in the slices versus superfusion time. In many experiments the medium was changed to another (K^+ 50 mM, antagonists) at 30 min and rate constants then calculated for the time interval of 32–40 min.

Statistical analyses

The presence of statistically significant differences between the sample means was detected by variance analysis. Comparisons of individual means were made by Hartley's sequential method of testing.

Results

Normoxia

The basal and K^+-stimulated release of [^{3}H]taurine from brain stem slices from 7-day-old mice was not affected under normoxic conditions by the tested adenosine receptor agonists and transport inhibitors (data not shown). In the adults the basal initial release (k_1) was significantly enhanced in the presence of the adenosine receptor A_1 agonist CHA (1 μM) (Fig. 1). This effect was abolished by the A_1 receptor selective antagonist DPCPX (1.0 μM). The A_{2a} receptor agonist CGS 21680 (10 μM) (Fig. 1) was without effect. The unselective adenosine A_1 and A_2 receptor and P_1 purine receptor antagonist 8-PT and the potent adenosine transport inhibitor NBTI enhanced the release. Another transport inhibitor, dipyridamole (10 μM), which also selectively inhibits phosphodiesterase PDE 5, had no effect (Fig. 1). None of the above adenosine compounds affected the potassium stimulation (50 mM K^+) of taurine release between 30 and 50 min in the adults (data not shown).

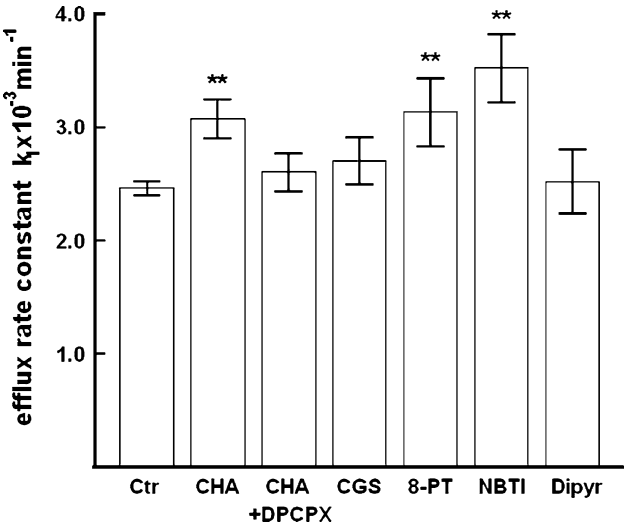

Fig. 1 Effects of adenosine compounds on taurine release from brain stem slices from adult mice under normal conditions. The *bars* show efflux rate constants k_1 (20–30 min) as follows: Ctr, normal conditions (control), the A_1 receptor agonist N^6-cyclohexyladenosine (CHA, 1.0 μM), CHA together with the A_1 receptor antagonist 8-cyclopentyl-1,3-dipropylxanthine (DPCPX, 1.0 μM), the A_{2a} receptor agonists 2-*p*-(2-carboxyethyl)phenylamino-5′-*N*-ethylcarboxamidoadenosinehydrochloride (CGS 21680, 10 μM), the A_1 receptor antagonist 8-phenyltheophylline (8-PT, 10 μM), and the adenosine transport inhibitors *S*-(4-nitrobenzyl)-6-thioinosine (NBTI, 50 μM) and dipyridamole (10 μM). The results are mean values ± SEM of 4–8 independent experiments. Significance of differences from the controls: **$P < 0.01$

Ischemia

Under ischemic conditions the basal taurine release was markedly enhanced. The constant k_2 significantly ($P < 0.01$) increased from $(2.02 \pm 0.33) \times 10^{-3}$ min^{-1} ($n = 7$) to $(3.48 \pm 0.34) \times 10^{-3}$ min^{-1} ($n = 12$) in 3-month olds and from $(0.35 \pm 0.5) \times 10^{-3}$ min^{-1} ($n = 8$) to $(1.74 \pm 0.21) \times 10^{-3}$ min^{-1} ($n = 11$) in 7-day olds. In the developing brain stem the basal release in ischemia was reduced by CHA, this effect being antagonized by DPCPX when added at the beginning of the superfusion (Fig. 2a). CGS 21680 also reduced the release in ischemia, which effect was abolished by the A_{2a} receptor antagonist DMPX (10 μM) (Fig. 2b). The adenosine transport inhibitors were ineffective (data not shown). In adults only CGS 21680 was

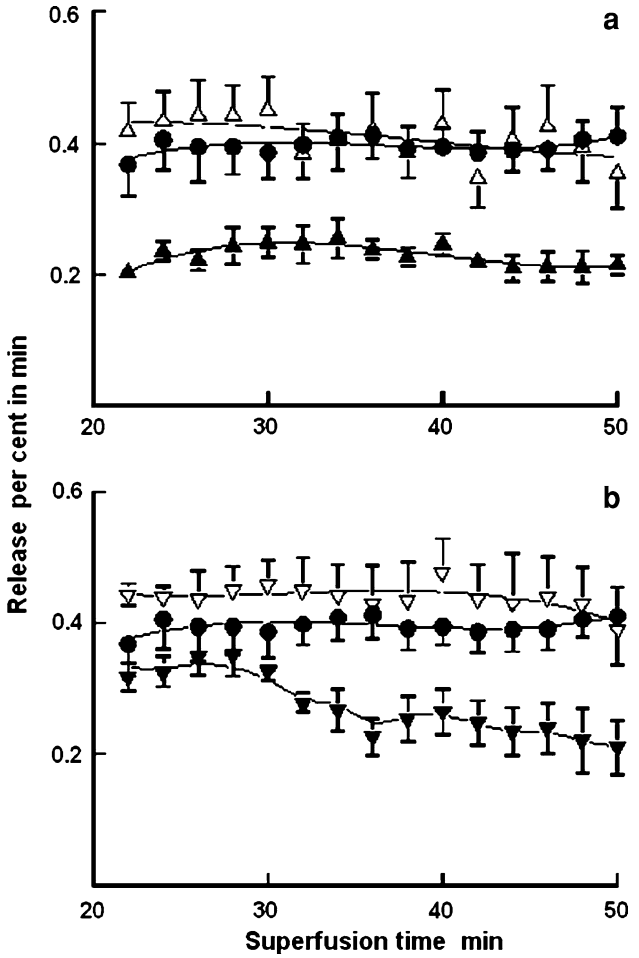

Fig. 2 Effects of adenosine receptor agonists on taurine release from brain stem slices from 7-day-old mice in ischemia (*filled circle*, control). **a** The effect of the A_1 receptor agonist CHA (1.0 μM) (*filled upright triangle*) and CHA together with the A_1 antagonist DPCPX (1.0 μM) (*open upright triangle*). **b** The effect of the A_{2a} receptor agonist CGS 21680 (10 μM) (*filled inverted triangle*) and CGS 21680 together with the A_{2a} receptor antagonist DMPX (10 μM) (*open inverted triangle*). The slices were exposed to the drugs from the beginning of superfusions. The results are mean values ± SEM of 4–6 independent experiments. In **a**, all points of the curve for CHA alone are significantly ($P < 0.01$) different from the corresponding points of the control and CHA + DPCPX curves. In **b**, the points of the curve for CGS 21680 alone are significantly ($P \leq 0.01$) different from the corresponding points of the CGS 21680 + DMPX curve and from the corresponding points of the control curve from 30 min onwards. Abbreviations (see Fig. 1)

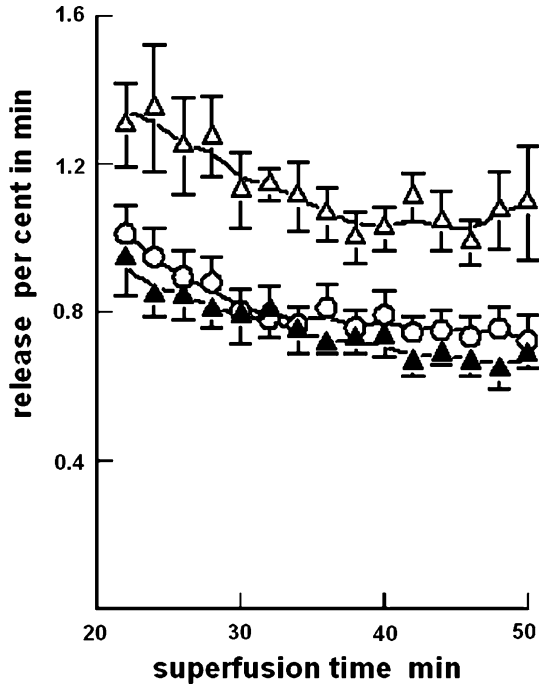

Fig. 3 Effects of the adenosine 10 μM CGS 21680 (*open upright triangle*) and 10 μM CGS 21680 together with the A_{2a} receptor antagonist 10 μM DMPX (*filled upright triangle*) on the taurine release (*filled circle*, control) from brain stem slices from adult mice in ischemia. The slices were exposed to the drugs from the beginning of superfusions. The results are mean values ± SEM of 4–6 independent experiments. All points of the CGS 21680 curve are significantly ($P < 0.01$) different from the corresponding points of the control and CGS 21680 + DMPX curves. Abbreviations (see Fig. 1)

effective, enhancing the release (Fig. 3). This increment was abolished by the antagonist DMPX. The adenosine transport inhibitors had no effects (data not shown).

Potassium stimulation in ischemia

K^+ stimulation evoked significantly ($P < 0.01$) more taurine release only in developing mice (0.35 vs. 3.30) × 10^{-3} min^{-1} (cf. above and Table 1). The K^+-stimulated taurine release in ischemia was reduced by CHA in the 7-day-old mice, which effect was again attenuated by the antagonist DPCPX ($P < 0.05$). CGS 21680 was without effect. In adults CHA had no effects, but CGS 21680 enhanced the release, which effect was abolished by DMPX ($P < 0.05$) added at the beginning of superfusion (Table 1). Transport inhibitors again had no effects (data not shown).

Discussion

The release of taurine in the developing and adult brain stem under normoxic conditions has been shown to resemble that of neurotransmitters or modulators. The release contains both Ca^{2+}-dependent and -independent components and is partly mediated by Na^+- and Cl^--dependent transporters operating outwards (Saransaari and Oja 2006). Taurine release is also modulated by cAMP second messenger systems, ionotropic and metabotropic glutamate receptors (Saransaari and Oja 2006) and nitric oxide-generating agents (Saransaari and Oja 2008b). It was now seen to be affected by adenosine receptor agonists and antagonists, both excitatory and inhibitory effects being

Table 1 Effects of adenosine agonists and antagonists on K^+-evoked taurine release from mouse brain stem slices in ischemia

Effector (μM)	Efflux rate constants k_2 ($\times 10^{-3}$ min^{-1}) ± SEM	
	3-Month old	7-Day old
Control	3.92 ± 0.26 (4)	3.30 ± 0.27 (4)
CHA (1.0)	4.10 ± 0.19 (8)	1.90 ± 0.12** (4)
+DPCPX (1.0)	–	2.96 ± 0.26$^{\#}$ (6)
CGS 21680 (10.0)	5.23 ± 0.34* (8)	3.34 ± 0.34 (4)
+DMPX (10.0)	4.09 ± 0.21$^{\#}$ (4)	–

The slices were superfused for 50 min. The effectors were added at the onset of superfusion and 50 mM K^+ at 30 min for the remaining 20 min. Number of independent experiments in parentheses

CHA N^6-cyclohexyladenosine; *DPCPX* 8-cyclopentyl-1,3-dipropylxanthine; *CGS 21680* 4-[2-{[6-amino-9-(*N*-ethyl-*β*-D-ribofuranuronamidosyl)-9H-purin-2-yl]amino}ethyl]benzanepropanoate; *DMPX* 3,7-dimethyl-1-propargylxanthine

Significance of differences from the controls *$P < 0.05$, **$P < 0.01$; the significance between the agonist and antagonist $^{\#}P < 0.05$

discernible. The effects were not similar in the mature and immature brain stem, being in fact opposite. Both A_1 and A_2 receptors modulate neuronal excitability and mRNAs encoding for A_1 and A_2 receptors are co-localized and co-expressed in this brain area (Cunha et al. 1994). While presynaptic A_1 receptors are mainly involved in attenuation of transmitter release, A_{2a} receptors mediate the psychomotor effects of adenosine agonists and antagonists and interact with the functions of other transmitters and modulators (Ribeiro 1999; Cunha 2008). Accordingly, A_{2a} receptors have been shown both to reduce and enhance transmitter release (O'Regan et al. 1992; Mori et al. 1996; Corsi et al. 1999). The adenosine receptors could thus modulate amino acid transmitter release in both positive and negative manner, depending on the receptor type activated and their interactions with each other.

Basal taurine release was not affected by the adenosine receptor agonists and transport inhibitors in the developing brain under normal conditions. Similar results have been obtained in vivo with microdialysis of the adult rat hippocampus and striatum (Heron et al. 1993; Goda et al. 1998), but in superfusion experiments in vitro A_1 receptor activation has depressed basal taurine release in the hippocampus of 7-day-old mice in a receptor-mediated manner (Saransaari and Oja 2000b). On the other hand, in the adult brain stem A_1 receptors seem to regulate basal taurine release, since the selective receptor agonist CHA was able to enhance it. This effect was blocked by the selective A_1 receptor antagonist DPCPX (Klotz 2000), indicating the involvement of receptors, though the effect could not be seen with the less specific antagonist 8-PT (Connolly et al. 1993). Taurine could participate in the tonic inhibition of synaptic transmission evoked by stimulation of A_1 receptors, as demonstrated in several brain areas (see Pedata et al. 2007). Adenosine A_{2a} receptors appear not to be involved in taurine release at all in the brain stem under normal conditions, since the agonist CGS 21680 was without effect in both adult and developing mice. Likewise only very minor effects have been detected in the hippocampus (Saransaari and Oja 2000b). In the cultured astroglial cells from the neurohypophysis, pituicytes, adenosine A_{2b} receptors mediate inhibition of taurine release (Pierson et al. 2007).

Taurine release in the brain stem was greatly enhanced in ischemic conditions in both immature and mature mice, as in higher brain areas (Saransaari and Oja 2007, 2008b, 2009; Oja and Saransaari 2009). The present attenuation of both basal and K^+-stimulated release in the 7-day-old brain stem in ischemia by the A_1 receptor agonist CHA, blocked by the antagonist DPCPX, is in contrast to the situation in the hippocampus, where adenosinergic compounds have no marked effects on taurine release in developing mice (Saransaari and Oja 2000b). Ischemia causes neuronal and glial cell swelling, resulting in substantial extracellular increases in certain amino acids, including glutamate, aspartate, and taurine (Phillis et al. 1997). However, swelling in ischemia occurs rapidly and thence induced diffusion of amino acids through anion channels mainly only during preincubation and at the onset of final incubation. A part of the release could also result from unspecific leakage through cellular membranes. This is not likely, however, since the present ischemic incubation conditions have been shown not to cause nonspecific membrane damage, e.g., liberation of intracellular lactate dehydrogenase (Saransaari and Oja 2004b). The enhancement of taurine release by the selective adenosine transport inhibitor NBTI is apparently due to an enforcement of the effect of extracellular adenosine whose sequestration into the cells is blocked (Thorn and Jarvis 1996). The same effect of the other inhibitor, dipyramidole, seems to be overshadowed by the other biological actions of this compound.

Adenosine A_1 receptor agonists have been shown to protect neuronal cells against ischemic damage in vivo by depressing both the basal and K^+-evoked release of excitatory amino acids (Heron et al. 1992, 1994; Goda et al. 1998). However, in some studies adenosinergic A_1 compounds have not affected glutamate accumulation (Heron et al. 1993), but have suppressed the ischemia-induced GABA release (O'Regan et al. 1992). The reduction in extracellular taurine levels by adenosine A_1 receptor activation may not be beneficial under ischemic conditions, not contributing to protection against excitotoxicity in the immature brain stem. On the other hand, activation of both ionotropic and metabotropic glutamate receptors together with NO effects greatly enhance taurine release in the brain stem in ischemia, particularly in developing animals (Saransaari and Oja 2008b, 2009).

The involvement of adenosine A_{2a} receptors in ischemia is obvious in the brain stem, since the basal and K^+-stimulated release in adults and the basal release in developing mice were enhanced by the specific A_{2a} agonist CGS 21680, which effects were blocked by the antagonist DMPX. This is again in contrast to the release in the hippocampus, where these receptors have had only minor effects in ischemia (Saransaari and Oja 2000b). The A_{2a} receptors have been held to have a crucial role, since they interact with multiple receptors and hence affect neurotransmitter release (Ribeiro 1999). Moreover, it is known that A_{2a} receptor antagonists exert neuroprotective effects in brain ischemia, probably by reducing glutamate outflow from neurons and glial cells (Pedata et al. 2007; Cunha 2008). A_{2a} receptor activation has generally enhanced the release of excitatory amino acids in normoxia (see Ribeiro 1999), while both stimulatory and inhibitory effects have been seen for example on GABA release in different brain areas (Kirk and Richardson 1995; Cunha and Ribeiro 2000). In ischemia adenosine receptor agonists have inhibited GABA release in the rat cerebral cortex (O'Regan et al. 1992) and mouse hippocampal slices (Saransaari and Oja 2005). It thus appears that in the adult brain stem A_{2a} receptor activation is able to provide neuroprotective effects by releasing more taurine in ischemia.

Conclusions

The basal taurine release in the brain stem is modulated by the adenosine A_1 receptor agonist CHA only in adults in normoxia. Potentiation of the release could aid in the maintenance of homeostasis in this brain area. In ischemia, CHA depresses both basal and K^+-stimulated taurine release in 7-day-old mice in a receptor-mediated manner, the A_{2a} receptor agonist CGS 21680 being also inhibitory. The two basically neuroprotective compounds, taurine and adenosine, may not cooperate in the prevention of ischemic neuronal damage. On the other hand, the A_{2a} receptor agonist enhances taurine release in the adult brain stem in ischemia, both basal and K^+-stimulated release being affected. In this case elevated levels of taurine could be beneficial, protecting against hyperexcitation and excitotoxicity.

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