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The effects of adenosine A_3 receptor stimulation on seizures in mice

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Abstract

We have previously shown that acute preischemic adenosine A_3 receptor stimulation results in an increased postischemic damage, while chronic stimulation of this receptor diminishes it. Since several pathophysiological phenomena are common for both ischemia and seizures, we have explored the effect of acute and chronic administration of the adenosine A_3 receptor selective agonist IB-MECA (N^6-(3-iodobenzyl) adenosine-5'-*N*-methylcarboxamide) prior to seizures induced by *N*-methyl-D-aspartate (NMDA), pentamethylenetetrazole, or electric shock. At 100 μg/kg, acutely injected IB-MECA was protective in chemically but not electrically induced seizures. In chronic administration of IB-MECA, significant protection against chemically induced seizures was obtained in all studied measures, i.e., seizure latency, neurological impairment, and survival. Although threshold voltage was unchanged in electrically induced seizures, a chronic regimen of IB-MECA significantly reduced postepileptic mortality. Since the combination of an arteriole-constricting compound 48/80 and hypotension-inducing clonidine injected prior to NMDA results in a significant protection against seizures, and since acute stimulation of adenosine A_3 receptor causes both arteriolar constriction and severe hypotension, there is a possibility that the protection obtained by the acutely administered drug may result from inadequate delivery of chemoconvulsants to the brain. It is, however, unknown whether the protective effect of chronically administered IB-MECA is related to the effect of the drug on blood flow, neuronal mechanisms, or both.

Keywords: Seizure; Adenosine A_3 receptor; Protection; (Mouse)

1. Introduction

The presence of adenosine A_3 receptors has been demonstrated in the rat (Zhou et al., 1992), gerbil (Ji et al., 1994), sheep (Linden et al., 1993), and human (Salvatore et al., 1993) brain. Although the biological significance of adenosine A_3 receptors is ill-defined, it is known that in vitro stimulation of adenosine A_3 receptors results in inhibition of adenylate cyclase (Zhou et al., 1992), and in stimulation of phospholipase C followed by formation of inositol 1,4,5-trisphosphate (IP_3 (Ramkumar et al., 1993; Ali et al., 1990)). Physiological in vivo responses include induction of heart rate-independent, prolonged hypotension in rats (Carruthers and Fozard, 1993; Fozard and Carruthers, 1993; Von Lubitz and Jacobson, unpublished), vasoconstriction (Doyle et al., 1994), and depression of locomotor activity in mice (Jacobson et al., 1993). Recently, it has also been shown that acute stimulation of adenosine A_3 receptors may play a significant role in the generation of postischemic brain damage in gerbils (Von Lubitz et al., 1994c). However, in view of diverging properties of adenosine A_3 receptors in different species (Salvatore et al., 1993; Ji et al., 1994), it is unclear whether these responses constitute a typical effect of adenosine A_3 receptor stimulation or are species-specific.

We have shown in gerbils that preischemic stimulation of adenosine A_3 receptors with a selective adenosine A_3 receptor agonist, N^6-(3-iodobenzyl) adenosine-5'-*N*-methylcarboxamide (IB-MECA (Gallo-Rodriguez et al., 1994)), produces a regimen-dependent effect, i.e., acute administration worsens, while chronic treat-

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ment improves the outcome of brain ischemia of moderate intensity (Von Lubitz et al., 1994c). Since several pathophysiological processes (e.g., activation of phospholipases A_2 and C, formation of IP_3) are typical of both cerebral ischemia and seizures (Bazan, 1989), we investigated the effect of acute and chronic administration of IB-MECA on the outcome of seizures. The effects of IB-MECA were studied in models in which seizures were elicited using different mechanisms, i.e., neuronal hyperactivation (*N*-methyl-D-aspartate (NMDA)-evoked seizures), perturbation of γ-aminobutyric acid (GABA)-mediated inhibition (pentamethylenetetrazole-induced convulsions (Rehavi et al., 1982)), and generalized convulsions generated by graded electric shock (Mastropaolo et al., 1992).

2. Materials and methods

Male C57Bl/J5 mice (Jackson Laboratory, Bar Harbor, ME, USA) weighing 35 g were used in this study.

2.1. Drugs and their administration

2.1.1. Studies of adenosine A_3 receptor agonist followed by chemoconvulsants

All drugs were injected i.p. using a 25 gauge hypodermic needle. The adenosine A_3 receptor agonist N^6-(3-iodobenzyl)adenosine-5′-*N*-methylcarboxamide (IB-MECA) was dissolved in a 20:80 v/v solution of Alkamuls 620 (Rhône-Poulenc, Cranbury, NJ, USA) and injected either acutely or chronically. In the acute regimen, IB-MECA was given at 10, 50, or 100 μg/kg ($n = 10$/group). After establishing the dose response for chemically induced seizures in the acute regimen, the dose characterized by the highest efficacy in all studied measures (100 μg/kg) was selected for the acute administration in studies of electroconvulsive shock ($n = 10$). The same dose was also chosen for chronic administration of IB-MECA (daily injections for 6 weeks, $n = 10$). Saline-dissolved (16 mg/ml) *N*-methyl-D-aspartate (NMDA) (Research Biochemicals International, Natick, MA, USA) was given acutely at 60 mg/kg, while acute injections of saline-dissolved pentamethylenetetrazole (Aldrich, Milwaukee, WI, USA) were given at 75 mg/kg ($n = 10$ (Rehavi et al., 1982)).

In the acute regimen, IB-MECA was injected 15 min prior to the administration of NMDA or pentamethylenetetrazole. In the chronic regimen, convulsants were administered 24 h after the last injection of IB-MECA. Both in NMDA ($n = 15$) and pentamethylenetetrazole ($n = 10$) control animals, the vehicle was used instead of IB-MECA. Since previous studies failed to show a statistically significant impact of prior acute or chronic vehicle administration on the intensity of subsequent NMDA-evoked seizures (Von Lubitz et al., 1993,1994a), the vehicle was given accordingly to the chronic schedule of IB-MECA.

2.1.2. Studies of hypotensive and vasoconstricting agents followed by chemoconvulsants

Experiments with IB-MECA and chemoconvulsants revealed that, contrary to the extensive mortality following acute administration of IB-MECA prior to cerebral ischemia, 100 μg/kg of the drug given prior to NMDA resulted in a complete elimination of deaths observed when NMDA was given alone. Since adenosine A_3 receptor agonists produce both hypotension (Fozard and Carruthers, 1993; Von Lubitz et al., in press) and vasoconstriction (Doyle et al., 1994), a possibility thus existed that the elimination of convulsions by IB-MECA might have resulted from an impaired drug delivery to the brain rather than from a direct anticonvulsant effect of the drug. To test this hypothesis, mice ($n = 10$/group) were administered 500 μg/kg of either saline-dissolved clonidine (RBI, Natick, MA, USA), an arteriole-constricting and histamine-releasing compound 48/80 (Sigma, St. Louis, MO, USA (Koibuchi et al., 1985; Doyle et al., 1994)), or both (500 μg/kg each), followed 15 min later by 60 mg/kg NMDA. Seizure latency and mortality were observed as in the preceding experiments.

2.2. Incremental electric shock

Graded D.C. current electric shocks lasting 0.3 s were generated by a Hittman electroconvulsive shock generator (Modcraft model B24-III) and administered via ear clip electrodes. Starting from 70 V, shocks were increased every 2 s in 10 V steps until either a full tonic seizure was elicited or a maximum voltage of 170 V was reached.

In the electric shock experiments, injections of IB-MECA were performed using the acute or chronic regimen described in the preceding section ($n = 10$/group). Controls ($n = 10$/ group) were injected with the vehicle using the same schedule.

2.3. Monitoring

All experiments were performed in a quiet room illuminated with low-intensity fluorescent lighting. Following injection of the convulsant or administration of electric shocks, mice were placed in individual transparent observation cages. In chemically induced seizures, the onset, duration, and the intensity of the subsequent neurological impairment were monitored for the following 15 min. The degree of neurological impairment was established using a 6-point scale (Von Lubitz et al., 1994a) where '1' indicated fully normal behaviour, and '6' the maximum intensity of seizure

Table 1
Percentage of animals with convulsive behavior appearing within 15 min of administration of vehicle and NMDA or either acute or chronic IB-MECA followed by NMDA

	Percent convulsing	P [a]	Average latency to seizures (s + S.E.M.)	P [b]
NMDA (60 mg/kg, $n = 15$)	80		244 ± 90	
IB-MECA + NMDA (10 μg/kg + 60 mg/kg, $n = 10$)	50	n.s.	581 ± 107	< 0.05
IB-MECA + NMDA (50 μg/kg + 60 mg/kg, $n = 10$)	10	< 0.05	12 [c]	n.a.
Acute IB-MECA + NMDA (100 μg/kg + 60 mg/kg, $n = 10$)	0	n.a.	n.a.	n.a.
Chronic IB-MECA + NMDA (100 μg/kg + 60 mg/kg, $n = 10$)	30	< 0.05	689 ± 108	< 0.05
Clonidine + NMDA (500 μg/kg + 60 mg/kg, $n = 10$)	70	n.s.	193 ± 39	n.s.
Compound 48/80 + NMDA (500 μg/kg + 60 mg/kg, $n = 10$)	50	< 0.05	264 ± 51	n.s.
Clonidine + compound 48/80 + NMDA (500 μg/kg + 500 μg/kg + 60 mg/kg, $n = 10$)	30	< 0.05	792 ± 79	< 0.05

[a] Fisher's test. [b] Dunnet's test. [c] Only one animal. Abbreviations: n.a. – non-applicable; n.s. – non-significant.

activity. Following the 15 min period of acute observation, animals were transferred to their home cages, and their behavior and mortality were monitored for the subsequent 24 h.

In the experiments using graded electric shock only the tonic seizure-producing voltage and survival during the subsequent 24 h were observed.

2.4. Temperature

Temperature effect of IB-MECA was measured using the Harvard (South Natick, MA, USA) rectal probe in animals subjected to a light halothane anesthesia. The temperature was measured either 15 min after acute administration of 100 μg/kg IB-MECA or 24 h after the last injection of the drug when given chronically ($n = 5$/group).

2.5. Statistical analysis

Dunnett's test was used to analyze seizure latency and the degree of neurological impairment, while Fisher's exact test with Bonferroni's correction was employed to analyze the mortality data. $P < 0.05$ was considered significant.

3. Results

3.1. Temperature effect of IB-MECA (100 μg/kg)

There were no significant temperature differences following either acute or chronic administration of the drug.

3.2. Acute experiments

3.2.1. IB-MECA (10, 50 or 100 μg/kg) and NMDA (60 mg/kg)

When compared to NMDA alone, acute administration of IB-MECA at 10 μg/kg prior to 60 mg/kg NMDA had no effect on either the incidence of seizures, or the degree of neurological impairment (Tables 1 and 2). However, administration of IB-MECA at 10 μg/kg caused a small but significant delay in the onset of convulsive behaviour (Table 1). In the group given IB-MECA at 50 μg/kg, seizures within the initial 15 min after administration of NMDA were present in only one animal, while a long-lasting locomotor depression characterized the rest of the group. Persistent myoclonic jerks were subsequently observed in two animals at ~ 30–45 min following the NMDA injection.

Table 2
Neurological impairment and mortality after administration of vehicle and NMDA or either acute or chronic IB-MECA followed by NMDA

	Impairment ± S.E.M.	P [a]	Mortality (% at 24 h)	P [b]
NMDA (60 mg/kg, $n = 15$)	3.5 ± 0.5		60	
IB-MECA + NMDA (10 μg/kg + NMDA, $n = 10$)	2.7 ± 0.6	n.s.	50	n.s.
IB-MECA + NMDA (50 μg/kg + 60 mg/kg, $n = 10$)	2.0 ± 0.5	n.s.	27	n.s.
Acute IB-MECA + NMDA (100 μg/kg + 60 mg/kg, $n = 10$)	1.4 ± 0.4	< 0.05	10	< 0.05
Chronic IB-MECA + NMDA (100 μg/kg + 60 mg/kg, $n = 10$)	1.8 ± 0.4	< 0.05	20	< 0.05
Clonidine + NMDA (500 μg/kg + 60 mg/kg, $n = 10$)	4.7 ± 0.6	n.s.	70	n.s.
Compound 48/80 + NMDA (500 μg/kg + 60 mg/kg, $n = 10$)	1.7 ± 0.9	< 0.05	30	< 0.05
Clonidine + compound 48/80 + NMDA (500 μg/kg + 500 μg/kg + 60 mg/kg, $n = 10$)	1.7 ± 0.9	< 0.05	30	< 0.05

[a] Dunnett's test. [b] Fisher's test with Bonferroni's correction. Abbreviation: n.s. – non-significant.

Table 3
Onset of convulsive behaviour, degree of neurological impairment, and mortality in animals treated with vehicle and PMT or either acute or chronic IB-MECA followed by PMT

	Onset (s) (±S.E.M.)	Impairment (±S.E.M.)	Mortality (%)				P [b]
			< 15 min	0.4–5 h	> 5 h	Overall	
PMT (75 mg/kg, $n = 10$)	74 ± 12	5.0 + 0.5	100	0	0	100	
Acute IB-MECA + PT (100 μg/kg + 75 mg/kg, $n = 10$)	112 ± 10 [a]	4.1 + 0.5	40	0	10	50	< 0.05
Chronic IB-MECA + PT (100 μg/kg + 75 mg/kg, $n = 10$) [b]	120 ± 9	3.3 + 0.5 [a]	40	10	0	50	< 0.05

[a] $P < 0.05$, Student-Newman-Keuls test. [b] Fisher's exact test with Bonferroni's correction. Abbreviation: PMT – pentamethylenetetrazole.

In the 10 μg/kg IB-MECA group, the mortality approached very closely that attained with NMDA alone, and all deaths occurred within 15 min following administration of NMDA (Table 2). However, in the 50 μg/kg IB-MECA group only one animal died within that time (12 s). The two subsequent deaths in that group (animals with myoclonic jerks) occurred at ~ 1 h after injection of NMDA.

At 100 μg/kg IB-MECA was protective in all studied measures (Tables 1 and 2). Although occasional scratching was present in some animals, clinically manifested seizures were completely absent (Table 1). Neurological disturbances accompanying acute IB-MECA at 100 μg/kg followed by NMDA at 60 mg/kg were limited to a period of lethargic behavior lasting 45–60 min after the injection of NMDA. During this period animals were fully responsive to external stimuli (sound, touch). A noxious stimulus (touch or tap with the tip of a pencil) caused a rapid translocation followed by a renewed period of locomotor quiescence. While moving, the gait of all animals appeared to be fully normal. The mortality was 10%, with the solitary death occurring 25 min after administration of NMDA.

3.2.2. IB-MECA and pentamethylenetetrazole

Administration of pentamethylenetetrazole alone resulted in the death of all animals within 15 min. When IB-MECA preceded the convulsant, the onset of seizures and overall mortality were significantly reduced. There was no effect on the neurological impairment (Table 3).

3.2.3. Clonidine, compound 48/80, and NMDA

Administration of clonidine prior to NMDA had no effect on either the incidence of seizures or their latency. Moreover, although the difference was statistically insignificant, both neurological impairment and mortality were numerically higher than in the group given NMDA alone (Tables 1 and 2). Although the pretreatment with the arteriole-constricting compound 48/80 did not have a significant effect on seizure latency, the number of convulsing animals was significantly reduced (Table 1). Both neurological impairment and mortality were significantly diminished in that group (Table 2). Following co-treatment with clonidine and compound 48/80 prior to the injection of NMDA, significant protection was observed in all studied measures, and all values were statistically indistinguishable from those observed when IB-MECA was given chronically (Tables 1 and 2).

3.2.4. Electric shock

Acute administration of IB-MECA resulted in an insignificant increase of threshold voltage (Table 4). Mortality remained unaffected.

3.3. Chronic experiments

3.3.1. IB-MECA (100 μg/kg) and NMDA (60 mg/kg)

Chronic administration of IB-MECA resulted in the reduction of neurological impairment (Table 2). Tonic seizures were observed in 20% of animals, but their onset was significantly delayed (Table 1). In the remaining animals, injection of NMDA rapidly elicited a protracted period of lethargic behaviour similar to that seen in animals injected acutely with IB-MECA at 100 μg/kg followed by 60 mg/kg NMDA (see above). Following chronic administration of IB-MECA, the mortality was reduced to 30% (Table 2).

Table 4
Vehicle followed by electric shock or acute or chronic IB-MECA followed by electric shock

	Threshold voltage (±S.E.M.)	P [a]	Mortality (% at 24 h)	P [b]
Acute vehicle + E.S. ($n = 10$)	91 ± 4		80	
Acute IB-MECA + E.S. ($n = 10$)	106 ± 10	n.s	70	n.s.
Chronic vehicle + E.S. ($n = 10$)	100 ± 11	n.s	80	n.s.
Chronic IB-MECA + E.S. ($n = 10$)	118 ± 13	n.s	30	< 0.05

[a] Dunnet's test. [b] Compared to chronic vehicle and E.S. Bonferroni's corrected Fisher's test. Abbreviations: E.S. – electric shock; n.s. – non-significant.

3.3.2. IB-MECA (100 μg / kg) and pentamethylenetetrazole (75 mg / kg)

Chronic injection of IB-MECA prior to 75 mg/kg pentamethylenetetrazole had no significant effect on either the onset of seizures or neurological impairment (Table 3). However, the mortality was significantly reduced. The reduction did not differ from that seen following acute administration of IB-MECA.

3.3.3. Electric shock

Chronic treatment with IB-MECA produced no significant changes in threshold voltage although the postictal mortality was significantly reduced (Table 4).

4. Discussion

The protective effect of adenosine A_1 receptor stimulation against seizures elicited by different means has been described several times (for review, see Dragunow, 1991), Cellular mechanisms triggered in response to activation of adenosine A_1 receptors and most likely responsible for reduced seizure susceptibility are also well known (Dragunow, 1991; Marangos and Miller, 1991; Von Lubitz and Marangos, 1992). This is the first report indicating that similar protection can be obtained through chronic stimulation of the newly discovered adenosine A_3 receptors.

Jacobson et al. (1993) showed that in mice IB-MECA is 50 times more potent at adenosine A_3 receptors than at either adenosine A_1 or A_{2A} sites. The same authors also demonstrated that locomotor depression caused by administration of 100 μg/kg IB-MECA is not reversed by administration of saturating doses of highly selective antagonists of either adenosine A_1 or A_{2A} receptors (Jacobson et al., 1993). In gerbils (Von Lubitz et al., 1994c), the prolonged (> 60 min, Von Lubitz and Jacobson, unpublished) hypertensive effect induced by an acute administration of 1.0 mg/kg of a potent, non-selective adenosine A_1/A_2 but not A_3 receptor antagonist 8-[4-[[[(2-aminoethyl)amino]carbonyl]methyl]oxy]phenyl]-1,3-dipropylxanthine (XAC (Jacobson et al., 1993)), is completely reversed by 100 μg/kg IB-MECA given 15 min after XAC. On the other hand, profound and long-lasting hypotension induced by acute injection of 100 μg/kg IB-MECA is not affected by 1.0 mg/kg XAC injected 15 min after IB-MECA (Von Lubitz et al., 1994c). These data indicate that IB-MECA acts selectively at adenosine A_3 receptors rather than a combination of adenosine A_3, A_1, and/or A_2 sites. Since adenosine A_3 receptors in small rodents have very similar ligand binding properties (Ji et al., 1994), it is likely that the effects of acutely administered IB-MECA described in this paper are the consequence of the interaction of the drug with adenosine A_3 receptors rather than with any other adenosine receptor subtype.

Amelioration of postconvulsive outcome by IB-MECA is non-specific and independent of the mechanism involved in seizure generation (i.e., hyperstimulation of NMDA receptors, interruption of GABAergic inhibition, or generalized convulsions elicited by electric shock). The results of the present study also indicate that the protection seen after the acute administration of IB-MECA may be also related to events other than the direct interaction of the drug with cerebral adenosine A_3 receptors.

Agonist stimulation of rodent adenosine A_3 receptors results in a rapidly ensuing, substantial, and long-lasting hypotension (Fozard and Carruthers, 1993; Von Lubitz et al., 1994c; see also review by Linden, 1994). Moreover, constriction of arterioles in hamster cheek pouch preparation has been demonstrated following exposure to 1 μM of a nonspecific adenosine A_3 receptor agonist N^6-(3-iodo-4-aminobenzyl)adenosine (I-ABA (Linden, 1994)). Yet, although both NMDA and pentamethylenetetrazole were administered 15 min following IB-MECA, i.e. at a time when the hypotensive effect of IB-MECA is at its maximum (Von Lubitz et al., 1994c, and unpublished), the results obtained with clonidine indicate that hypotension has no effect on the delivery of chemoconvulsants to the brain. This conclusion is in good accord with the observations of several previous authors (for a review, see Fenstermacher, 1989) showing that blood flow affects cerebral concentration of primarily lipophilic agents, while the uptake of highly polar compounds, such as NMDA, depends mainly on their permeability through the blood-brain barrier. It is, therefore, quite unlikely that IB-MECA-induced perturbations of cerebral blood perfusion produce more than a minimal effect on the final intracerebral concentration of NMDA.

Striking improvement of protection against NMDA-induced seizures resulting from the administration of the arteriolar constrictor compound 48/80 either alone or in combination with clonidine indicates, however, that the protective effect of acutely administered IB-MECA may rest with the drug-induced effect on the time-dependent plasma concentration of NMDA, and hence, the amount of the agent available at any given time for uptake into the brain. In view of the results of Doyle et al. (1994) who showed a profound vasoconstricting effect of adenosine A_3 receptor agonists, it is possible that the reduction of both blood pressure and blood vessel diameter elicited by IB-MECA results in a diminished peripheral absorption of NMDA (i.e., at the site of its i.p. injection) leading to the plasma concentration of NMDA that is below the level required to produce seizures.

Although further studies are necessary to clarify the issue of rheological perturbations as a source of the

anticonvulsant effect of acutely administered IB-MECA, several observations support this possibility. Thus, when animals were injected with 10 μg/kg IB-MECA followed by 60 mg/kg NMDA, the mortality rate was statistically indistinguishable from that seen with the vehicle and NMDA at 60 mg/kg (Von Lubitz et al., 1994a, and the present study). On the other hand, when 100 μg/kg IB-MECA preceded 60 mg/kg NMDA, the mortality was entirely absent. Moreover, prolonged locomotor depression observed in all mice was indistinguishable from that elicited by a subconvulsant dose of 30 mg/kg NMDA alone (also described in our previous study (Von Lubitz et al., 1993)). Elevation of the NMDA dose to 125 mg/kg entirely abolished the protective effect of the previously injected IB-MECA, and the ensuing mortality was statistically indistinguishable from that seen with 125 mg/kg NMDA alone. Remarkably, however, the delay in the onset of seizures was very significantly greater (unpublished). It appears, therefore, that providing the initially administered dose of the convulsing agent is sufficiently high, the rheological effects of adenosine A_3 agonists (Linden, 1994; Von Lubitz et al., 1994c) may slow down the delivery rate of the convulsant but fail to prevent the ultimate build-up of its concentration within the brain to the level sufficient to trigger epileptic activity.

Since the dose range separating non-convulsant from convulsant doses of NMDA is very narrow (Leander et al., 1988; Von Lubitz et al., 1993, and unpublished data), a converse argument may apply to lower doses of NMDA (i.e. 60 mg/kg) administered after IB-MECA. Thus, it is quite conceivable that due to its vasoconstricting properties, even a small IB-MECA-mediated decrease in the absorption of NMDA following its i.p. injection may bring the plasma concentration of the chemoconvulsant to the subepileptogenic level, and result in an apparent protection.

The results of the experiments in which acutely administered IB-MECA was entirely ineffective in protecting against electroshock-induced seizures offer further support of the notion that amelioration of the outcome observed after acute administration of the adenosine A_3 receptor agonist may be based upon pharmacokinetic phenomena rather than a direct effect of the drug.

Although the protective effect of chronically administered IB-MECA is consistent in both chemically and electrically evoked seizures, its dependence on drug-induced changes in the cerebral blood perfusion cannot be excluded. We have recently demonstrated (Von Lubitz et al., 1994c) that chronic treatment with IB-MECA causes a slight but significant hypertension. Hence, the ameliorative effect of chronically injected IB-MECA demonstrated in this study may depend on the drug-mediated maintenance of more than adequate cerebral blood perfusion coinciding with the extreme metabolic stress caused by the epileptic activity (Chapman et al., 1977).

Whether protective actions of chronically administered IB-MECA include direct interaction of the drug with neurons is entirely unclear. We have previously argued that such a contribution is important in the context of ameliorative consequences of chronic adenosine A_3 receptor stimulation in cerebral ischemia (Von Lubitz et al., 1994b,c), where maintenance of suitable cerebral blood flow alone is frequently insufficient to reduce postischemic damage (Bengtsson and Siesjö, 1990; Martz and Hoff, 1990). In seizures, despite maintained cerebral blood perfusion (Chapman et al., 1977), several pathophysiological events are identical to those observed during and immediately after brain ischemia (Siesjö, 1981; Bazan, 1989). Hence, one may envisage the existence of purely neuronal processes that are facilitated by chronic stimulation of cerebral adenosine A_3 receptors and assist in recovery following a seizure episode. However, whether IB-MECA is, indeed, capable of inducing such processes, together with their nature remains to be demonstrated.

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