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Review

Adenosine and cerebral ischemia: therapeutic future or death of a brave concept? [1]

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Abstract

Numerous studies have consistently shown that agonist stimulation of adenosine A_1 receptors results in a significant reduction of morbidity and mortality associated with global and focal brain ischemia in animals. Based on these observations, several authors have suggested utilization of adenosine A_1 receptors as targets for the development of clinically viable drugs against ischemic brain disorders. Recent advent of adenosine A_1 receptor agonists characterized by lowered cardiovascular effects added additional strength to this argument. On the other hand, although cardioprotective, adenosine A_3 receptor agonists proved severely cerebrodestructive when administered prior to global ischemia in gerbils. Moreover, stimulation of adenosine A_3 receptors appears to reduce the efficacy of some of the neuroprotective actions mediated by adenosine A_1 receptors. The review discusses the possible role of adenosine receptor subtypes (A_1, A_2, and A_3) in the context of their involvement in the pathology of cerebral ischemia, and analyzes putative strategies for the development of clinically useful strategies based on adenosine and its receptors. It also stresses the need for further experimental studies before definitive conclusions on the usefulness of the adenosine concept in the treatment of brain ischemia can be made.

Keywords: Adenosine; Adenosine receptor; Cerebral ischemia; Stroke; Treatment

1. Introduction

Reading the reviews of current therapies for ischemic stroke, one cannot escape a sense of excitement at the progress that has been made in understanding its underlying mechanisms, and of gloom caused by our continuing inability to design its effective treatment. Extensive clinical trials of drugs that have convincingly demonstrated amelioration of stroke-induced damage in animal models (Koroshetz and Moskowitz, 1996; Caplan, 1997; Ginsberg, 1997) ended with thrombolysis as the only option that continues to show promise (Zülküf Önal and Fisher, 1997). Yet, even here, there is a dark side. Inclusion criteria are highly restrictive (e.g., Selman et al., 1997), allowing only a relatively limited number of acute stroke patients to benefit from this therapy (Albers, 1997), and the significant risk of haemorrhagic episodes and further morbidity continues to cause concern (del Zoppo et al., 1998).

The very modest awareness of the early signs of stroke among the medically untrained population (Pancioli et al., 1998) prevents rapid interception of the emerging episode and, combined with the paucity of clinically available means of pharmacological treatment, results in a high stroke-related mortality (Hund et al., 1995). Hence, billions of dollars are spent worldwide on primarily supportive treatment of uncertain outcome, and on the subsequent need for extensive rehabilitation and continuous, sometimes lifelong, medical assistance (Jorgensen et al., 1997; Taylor, 1997; Kaste et al., 1998).

Historically, one of the major obstacles to the development of clinically effective treatment were the persistent attempts to develop narrow action profile drugs that were expected to perform almost miraculous therapeutic feats, but yet ameliorating, at times not very efficiently, only one of the many aspects of the human stroke. Inadequate animal testing (del Zoppo, 1995; Hunter et al., 1995), and often too willing extrapolation of experimental results to the clinical reality, proved another source of problems. Yet, either despite, or even more likely, due to the ensuing series of expensive and time consuming failures, new

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conceptual approaches emerged. Their rationale is based on precise targeting of the mechanistic, cerebro-topographic, and temporal events characteristic of stroke (Fisher, 1997), and, in similarity to the treatment of cancer, on multi-rather than single drug interventions (Fisher, 1995, 1997; Dyker and Lees, 1996).

Numerous authors, the present included (see reviews by Rudolphi et al., 1992; Sweeney, 1997; von Lubitz, 1997a) have hotly advertised adenosine and its receptors as a target for therapeutic implementation in the treatment of stroke. In theory, and maybe even in the experimental practice, the responses evoked by stimulation of adenosine receptors result in everything that an effective treatment of stroke would be required to do. There is reduction in the release of excitotoxic neurotransmitters, attenuation of *N*-methyl-D-aspartate (NMDA) receptors, vasorelaxation, antiinflammatory effects, reduction of metabolism, thus, also a moderate reduction of the body/brain temperature. But most importantly, there is, at least in animal models, an impressive reduction of neuronal damage and mortality hardly attained by any other drug. But there is also hypotension, uncertain therapeutic consequences of prolonged adenosine receptor stimulation, and the emerging possibility of conflicting effects elicited by adenosine itself. Thus, should we, or should we not?

2. Adenosine and brain

2.1. Formation and concentration of interstitial adenosine

Catabolic activity of several major metabolic pathways leads to the production of adenosine (Fredholm, 1997). At rest, extracellular ecto-5′-nucleotidases provide another significant source by converting released adenine nucleotides to adenosine (White and Hoehn, 1991; Higgins et al., 1994). However, during metabolic stress induced by elevated electrical activity, hypoxia, or ischemia, the bulk of adenosine originates from the intense degradation of ATP (Whittingham, 1990). Bidirectional equilibrative- and sodium gradient-dependent nucleoside transporters translocate cytosol-formed adenosine to the extracellular space (Cass, 1995; Guieu et al., 1996), although there are indications that the characteristics of adenosine outflow evoked by electrical stimulation may differ from those observed during ischemia (Latini et al., 1996a,b).

The resting concentration of adenosine is difficult to determine due to its very short half-life (Ontyd and Schrader, 1984), and the practical difficulties imposed by the available methods of measurement that invariably induce degradation of ATP to adenosine contaminating the results (von Lubitz and Marangos, 1990; Fredholm, 1997). For these reasons, even the best estimates obtained by means of indwelling microdialytic probes show a considerable span, with the steady state values of interstitial adenosine measured in awake rats varying between 30 and 300 nM (Ballarin et al., 1991). Ischemia, head injury, and seizures induce a rapid increase of adenosine concentration up to 30–100 times above the resting level (Hagberg et al., 1987; Phillis, 1990; During and Spencer, 1992; Bell et al., 1998).

In focal ischemia, the reduction of cerebral blood flow to 25 ml 100 g^{-1} min^{-1} is sufficient to elevate intracerebral concentration of adenosine (Matsumoto et al., 1992), although further depression of cerebral blood flow induces release of excitatory amino acids. However, since it has also been shown that activity-dependent release of adenosine (Mitchell et al., 1993) is closely related to the stimulation of NMDA and AMPA receptors (Hoehn and White, 1990a,b; Manzoni et al., 1994; Delaney and Geiger, 1998; Delaney et al., 1998), the control of ischemic/post-ischemic adenosine release (and of the maximum attainable levels) may be determined by a wide range of pathophysiological factors prevailing within a given volume of brain at any given time. The fact that free radicals are also involved in the liberation of adenosine (Carswell et al., 1997; Delaney et al., 1998) supports such probability even further.

2.2. Adenosine receptors

Adenosine acts at four receptor subtypes, A_1, A_{2A}, A_{2b}, and A_3 (Fredholm et al., 1994a). All subtypes belong to the superfamily of G-protein coupled receptors, with A_1 and A_3 interacting with G_j/G_o proteins, and A_{2A} and A_{2B} with G_S (Palmer and Stiles, 1997). In similarity with the majority of other G-protein coupled receptors, all adenosine receptor types are characterized by seven transmembrane helices (Palmer and Stiles, 1995).

The affinity of adenosine A_2 receptors for adenosine is lower than that of A_1 receptors, and their stimulation elevates, while activation of both adenosine A_1 and A_3 receptors reduces, the concentration of intracellular cAMP (van Calker et al., 1979; Zhou et al., 1992). In addition to their inhibitory effects on adenylate cyclase, and contrary to adenosine A_2 receptors, both adenosine A_1 and A_3 receptors are also characterized by their stimulatory effect on phospholipase C (Abbracchio et al., 1995). Adenosine affinity at adenosine A_3 receptors is the lowest among all subtypes.

Radioautographic studies have shown that adenosine A_1 receptors are particularly abundant in the hippocampus, I, IV, and VI laminae of the cortex, superior colliculus, and cerebellum (Goodman and Snyder, 1982; Jarvis and Williams, 1989). Although their location is both pre- and postsynaptic (Deckert and Jorgensen, 1988), they can be also found extrasynaptically on dendrites (Rivkees et al., 1995), and on the axonal fibers of the hippocampus and corpus callosum has also been demonstrated (Swanson et al., 1995a, 1998).

Both subtypes of adenosine A_2 receptors are found on the smooth muscle fibers and on the endothelial cells of

cerebral blood vessels (Kalaria and Harik, 1986). However, the densest population of high affinity neuronal adenosine A_{2A} sites is present in the striatum (Jarvis and Williams, 1989). Adenosine A_{2A} receptors have been also found on astrocytes and microglia, and low affinity adenosine A_{2B} receptors on astrocytes (Fiebich et al., 1996).

Adenosine A_3 receptors are distributed throughout the entire brain, but at a density that is significantly lower than that of the other subtypes (Ji et al., 1994). Although their specific cellular location is poorly known, they have been demonstrated on microglia (Fiebich et al., 1996), and in vascular smooth cells (Zhao et al., 1997). The presence of adenosine A_3 receptors on neurons is also suspected (Linden, 1994), and electrophysiological experiments confirm this assumption (Dunwiddie et al., 1997).

In similarity to other G-protein coupled receptors, prolonged exposure of adenosine receptors to their agonists results in desensitization and attenuation of the cellular responses despite uninterrupted stimulation of the receptor (Jacobson et al., 1996; Böhm et al., 1997; Palmer and Stiles, 1997; Hettinger et al., 1998). The characteristics of adenosine receptor desensitization appear to be tissue specific (Hettinger et al., 1998). In the brain, a prolonged exposure of adenosine A_1 receptors to the agonist results in the reduction of receptor density, and in a homologous desensitization of the agonist-induced inhibition of adenylyl cyclase (Hettinger et al., 1998), while heterologous interactions appear to predominate in the peripheral tissues (e.g., Parsons and Stiles, 1987; Green et al., 1990). Moreover, adenosine A_1 receptor half-life is significantly longer than that of other G-protein coupled receptor types (21 h vs. approximately 10 min for β_2-adrenoceptor (see Pippig et al., 1995), and its internalization time much slower (i.e., 50% sequestration following 24-h long exposure cerebellar granule cells to cyclopentyladenosine vs. maximum sequestration of β_2-adrenoceptors after only 10 min exposure to their agonist (e.g., von Zastrow and Kobilka, 1992; Hettinger et al., 1998)). Adenosine A_3 receptors contrast adenosine A_1 receptor subtype: although no data on brain receptors are available, studies using stably transfected Chinese hamster ovary (CHO) cells have shown that following 10 min exposure to the agonist, the process of desensitization may result in 30–40% reduction of the high affinity binding sites (Palmer and Stiles, 1995). The difference of adenosine A_1 and A_3 receptors in their respective desensitization patterns indicates that, despite similarity of their second messenger systems, the functions of either receptor subtype must be highly distinct and independent of each other (Palmer and Stiles, 1997).

Several authors have shown that cerebral ischemia and stroke reduce adenosine A_1 receptor density (Daval et al., 1989; Onodera et al., 1989; Åden et al., 1994; Nagasawa et al., 1994). Adenosine A_1 and A_2 receptors mRNA have been shown to decrease as well (Åden et al., 1994). In the animal models of stroke, the initial decrease in adenosine A_1 receptor density is slow during the first 24 h after reestablishment of the cerebral blood perfusion (Nagasawa et al., 1994). This may indicate that functional adenosine A_1 receptors are still present within the penumbra zone (the volume of 'incomplete infarction', Garcia et al., 1996) and represent an inviting therapeutic target (Bischofberger et al., 1997). In the selectively vulnerable regions, the disappearance of adenosine A_1 receptors following global ischemia is a much faster process (Daval et al., 1989; Onodera et al., 1989). In either case, the loss of receptors does not correspond to the loss of neurons, and sequestration rather than complete elimination of receptor units appears to take place within the initial 24 h following the arrest of cerebral circulation. The latter conclusion appears even more likely in view of the unchanged interactions of adenosine A_1 receptors with G-proteins observed despite attenuated effect on adenosine A_1-receptor mediated depression of adenylyl cyclase (Domanska-Janik et al., 1993). The ultimate loss of adenosine A_1 receptors is, most likely, related to the eventual degeneration of adenosine receptor mRNA (Åden et al., 1994), followed by the physical disappearance of the irretrievably damaged neurons (Onodera and Kogure, 1985; Araki et al., 1992).

Postischemic loss of functional adenosine A_1 receptors may have a substantial impact on the neuronal capacity to withstand the stress of ischemia. Alzheimer et al. (1993) have shown that pharmacological suppression of these receptors induces long-lasting disinhibition of the inhibitory tonus in the CA3 sector of the hippocampus. Loss of the ability to modulate glutamate release (Fredholm and Dunwiddie, 1988; Katchman and Hershkovitz, 1993, see the following section) caused by postischemic reduction in the density of adenosine A_1 receptors at the affected terminals of Schaffer's collaterals can be expected to evoke similar disinhibition,. Hence, the consequent exposure of postsynaptic neurons in the CA1 sector to a continuously elevated presence of neurotoxic glutamate will rapidly lead to their irreparable damage. It is likely that adenosine A_1 receptor loss and the subsequent disinhibition of the excitatory afferent input may also constitute one of the key mechanisms underlying the phenomenon of selective vulnerability typical of global ischemia (von Lubitz et al., 1995a,b).

Klishin et al. (1994, 1995) have shown that blockade of adenosine A_1 receptors changes the ratio of NMDA- vs. non-NMDA receptor-mediated component of excitatory postsynaptic currents (see also the review by Hammond et al., 1994) in a Ca^{2+}/Mg^{2+}-dependent manner. Once the alteration has been attained, it becomes irreversible, and no longer depends on the activity of adenosine A_1 receptors. Although increased serum Ca^{2+}/Mg^{2+} ratio has been demonstrated in human patients early after stroke (Altura et al., 1997), it is uncertain whether similar changes exist within the affected brain volume itself. However, the changes of free intracerebral Mg^{2+} have been described in both percussion-induced (Vink et al., 1996) and closed head brain injury (Suzuki et al., 1997) models, in which

free Mg^{2+} concentration declined very rapidly followed by a slow (8 days) return to the preinjury level (Vink et al., 1996). Hence, it is tempting to speculate that the loss of adenosine A_1 receptors may be one of the reasons for a long lasting, low level activation of NMDA receptors contributing to the progressive increase of the damaged brain volume. Similar mechanism may also provide the link between stroke and the increased risk for the subsequent development of Alzheimer's disease (Kokomen et al., 1996). The possibility of altered inhibitory phenomena that induce persistent hypoactivation of NMDA receptors has been recently suggested by Olney et al. (1997) as one of the principal mechanisms participating in the development of Alzheimer's disease. Involvement of adenosine receptors as an element connecting stroke and subsequent Alzheimer's disease is currently investigated at our laboratory.

2.3. Electrophysiological and neurochemical effects of adenosine receptor stimulation

2.3.1. Adenosine A_1 receptors

Together with γ-aminobutyric acid (GABA), adenosine acting at A_1 receptors serves as the principal inhibitory neuromodulator in the brain (Kostopoulos and Phillis, 1977). While adenosine A_2 receptors appear to provide excitatory functions (Sebastiao and Ribeiro, 1996), the role of adenosine A_3 receptors in neuronal functions requires definition.

The inhibitory effect of adenosine A_1 receptor stimulation has a pre- and postsynaptic component. Activation of the presynaptic receptors reduces Ca^{2+} influx through the preferential inhibition of N-type and, possibly, Q-type channels (Yawo and Chuhma, 1993; Wu and Saggau, 1994). Inhibition of the presynaptic calcium currents decreases transmitter release (Prince and Stevens, 1992), and adenosine has been found to attenuate liberation of several neurotransmitters, e.g., glutamate, acetylcholine, dopamine, noradrenaline, serotonin, etc. (Fredholm and Dunwiddie, 1988). A Ca^{2+}-independent component of adenosine-mediated depression of neurotransmitter release has been also described (Scholz and Miller, 1992).

The postsynaptic effects consist chiefly of the enhancement of inward rectifying K^+ (Siggins and Schubert, 1981; Gerber et al., 1989; Alzheimer and ten Bruggencate, 1991; Segal, 1992), and voltage-dependent, GABA-independent Cl^- conductances (Mager et al., 1990). The concerted action of these mechanisms results in stabilization of the postsynaptic membrane potential and attenuation of NMDA receptor excitability (Schubert and Mager, 1991; de Mendonça et al., 1995).

Normoxic stimulation of adenosine A_1 receptors modulates synaptic strength by reducing the number of the released neurotransmitter quanta (Lupica et al., 1992). During ischemia, however, both pre- and postsynaptic effects are involved (de Mendonça and Ribeiro, 1993). Presynaptic hyperpolarizing actions of adenosine result in diminished release of excitatory neurotransmitters as shown by the preischemic administration of adenosine A_1 receptor antagonists that leads to a substantially increased concentration of excitatory amino acids in the extracellular space (Sciotti et al., 1992). Diminished availability of glutamate attenuates the intensity of postsynaptic NMDA receptor activation (Schubert and Mager, 1991) which, in turn, reduces postsynaptic influx of Ca^{2+}. Consequently, postsynaptic membrane potential stabilizes below the level necessary to activate voltage-regulated Ca^{2+} channels (Schubert and Kreutzberg, 1990), and to interrupt voltage-sensitive K^+ currents whose operation constitutes and important element of the protective hyperpolarizing complex (Segal et al., 1984).

Recently, Brundege and Dunwiddie (1996) described a process in which increased activity of the hippocampal postsynaptic pyramidal neuron enhances its own production of intracellular adenosine which, following transport to the extracellular space, acts as a retrograde messenger and inhibits the very same neuron's excitatory input. Under the normal conditions, the magnitude of such 'egotropic' inhibition by adenosine is substantial (adenosine released by a neuron is capable of inhibiting 80% of its excitatory responses; Brundege and Dunwiddie, 1996). As discussed below, during ischemia and postischemic recovery the importance of such inhibition may be drastically reduced.

The final aspect of adenosine-mediated depressant effects relevant to cerebral ischemia and its treatment is the inhibition of excitatory but not inhibitory synaptic transmission consequent to adenosine A_1 receptor activation (Yoon and Rothman, 1991; Fowler, 1993; Katchman and Hershkovitz, 1993). It has been also suggested that adenosine A_1 receptor-mediated enhancement of Cl^- conductance may be an important element in sustaining inhibitory efficacy of GABA (Schubert and Kreutzberg, 1990). The wide range of hyperpolarizing effects induced by stimulation of adenosine A_1 receptors indicates the possibility (von Lubitz, 1997a) that intraischemic activation of these receptors may constitute an important mechanism that delays the onset of hypoxic depolarization stage when most of the cerebrodestructive ischemic phenomena are initiated (Hansen, 1990; Obrenovich et al., 1990).

A number of studies demonstrated recently the involvement of adenosine A_1 receptors in phosphoinositol metabolism mediated through the activation of phospholipase C (reviewed by Fredholm et al., 1995). The importance of perturbed phosphoinositide metabolism in generation of postischemic injury, particularly through its effect on postischemic inflammatory processes, has been well documented (see reviews by Hallenbeck, 1996; Kogure et al., 1996). Hence, it is disturbing to note that adenosine (or adenosine A_1 receptor agonists) and bradykinin, a very powerful autacoid released during ischemia promoting both

blood–brain barrier opening and the development of brain edema (reviews by Wahl et al., 1996; Schilling and Wahl, 1997), produce synergistic effects on the release of inositol (1,4,5)-triphosphate (IP_3) from renal artery smooth muscle cells in vitro (Fredholm et al., 1995). Tissue-specific responses may be involved in this process, since in the CHO cells the highly selective adenosine A_1 receptor agonist N^6-cyclopentyladenosine (CPA) promotes IP_3 release (Megson et al., 1995), while in the hippocampus the same agonist administered at the concentration similar to that of the endogenous extracellular adenosine (10–300 nM) has a powerful inhibitory effect (Casalheira and Sebastiao, 1998). Moreover, selective adenosine A_1 receptor agonists diminished IP_3 release from cerebromicrovascular endothelium, despite the presence of another mediator of inflammation —histamine (Stanimovirovic et al., 1994).

Adenosine A_1 receptor-dependent activation of phospholipase C which is involved both in phosphoinositol and diacylglycerol (DAG) formation appears to depend, in similarity to other adenosine receptor-mediated processes (Lee et al., 1983), on the level of receptor expression (Biber et al., 1997). Hence, while adenosine A_1 receptor—phospholipase C (and D, see Fredholm et al., 1995) interactions may have a very important role in finely-tuned modulatory effects of adenosine, there is a possibility that their relevance is less critical under pathological conditions of cerebral ischemia. This conclusion is also supported by the fact that activation of phospholipase C requires abundant presence of the mediating $\beta\gamma$ G-protein subunits (Fredholm et al., 1995), whereas studies of the gerbil hippocampus indicate progressive postischemic decline of β subunits that reaches its maximum (28% reduction) 4 days after the occlusion (Suyama et al., 1995). These results clearly indicate that, due to their destructive potential, the effects resulting from adenosine A_1 receptor-induced activation of phospholipases C and D, and their eventual contribution to inflammatory processes seen in the postischemic brain (Clark et al., 1994; Fassbender et al., 1994), need further studies.

A limited number of recent papers describe involvement of adenosine A_1 receptors in nitric oxide (NO) synthesis, release, and signaling. Barth et al. (1997) have shown in the hippocampal slices that stimulation of both adenosine A_1 and A_{2A} receptors, either by the stable adenosine analogue 2-chloroadenosine or by a simultaneous application of both adenosine and adenosine deaminase inhibitor *erythro*-9-(2-hydroxy-3-nonyl) adenine (EHNA), induces elevated NO production, and causes significant neurotoxic damage within the slice. Adenosine itself, even when its concentration was raised to 500 μM, failed to produce the same effect. Since exogenously applied adenosine is rapidly metabolized, and the application of EHNA assures its more sustained presence in the extracellular space, the observations of Barth et al. (1997) indicate potential source of concern related to the eventual therapeutic uses of adenosine uptake or breakdown inhibitors.

Involvement of adenosine receptors in glial release of NO is controversial since Janigro et al. (1996) have shown its stimulation through the activation of both adenosine A_1 and A_{2A} receptors, while Brodie et al. (1998) indicated equally convincingly adenosine A_{2A} receptor-mediated inhibition of inducible nitric oxide synthase (iNOS) in C6 glial cells. However, these discrepancies may have been caused by the different cell systems used by either group. Finally, Broome et al. (1994) presented preliminary data on the involvement of adenosine A_1 receptors in the depression of synaptic transmission involving NO-cGMP mechanisms. In conclusion, and in similarity to inositol metabolism, the clarification of adenosine A_1 receptors involvement in NO synthesis and release is needed. The need is emphasized by the results presented by numerous authors who have shown that NO released during cerebral ischemia can be both highly protective and highly destructive, depending on the type of cells from which it is being released, and on the time of its release in relation to other phenomena taking place during the evolution of stroke evolution (see reviews by Farci and Brian, 1994; Brown, 1997; Iadecola, 1997).

2.3.2. Adenosine A_2 receptors

Although the recognition of adenosine involvement in NO-mediated vasodilation of cerebral vessels is relatively recent (Iadecola et al., 1994; Bhardwaj et al., 1995; Pellegrino et al., 1995; Stella et al., 1995), the principal role of adenosine A_{2A} receptors in the regulation of normoxic and hypoxic cerebral blood flow has been known for several years (reviews by Phillis, 1989, 1993; see also Pellegrino et al., 1995; Coney and Marshall, 1998). The participation of these receptors during postischemic reperfusion is far less certain (Wei and Kontos, 1993), despite the fact that a significant improvement of postischemic cortical blood flow has been described following either inhibition of adenosine transport by 4-nitrobenzylthioinosine (NBTI) in pigs (Gidday et al., 1996), or acute treatment with 2-[{2-aminoethylamino)-carbonylethylphenylethylamino]-5′-*N*-ethylcarboxoamidoadenosine (APEC) in gerbils (von Lubitz et al., 1995a,b).

Contrary to adenosine A_1 receptors, the neuronal actions of adenosine A_2 receptors are excitatory (Sebastiao and Ribeiro, 1996), and their stimulation results in calcium-dependent release of glutamate (O'Regan et al., 1992; Popoli et al., 1995) and acetylcholine (Kirk and Richardson, 1994; Brown, 1997) that may involve P-type channels (Umemiya and Berger, 1994). A_2 receptors are also involved in the modulation of GABA release (Kirk and Richardson, 1994, 1995; Mori et al., 1996). Consistent with these reports are the data from electrophysiological studies showing participation of adenosine A_2 receptors in the induction (but not maintenance) of long term potentiation (Sekino et al., 1991; Kessey et al., 1997).

The discovery of coexpression, colocalization (reviewed by Schiffmann and Vanderhaegen, 1995; Svenningsson et

al., 1997), and functional relationships (Ferré et al., 1992, 1997) between A_{2A} and dopamine D_2 receptors in neurons expressing enkephalin and dopamine D_2 receptors in the basal ganglia added new momentum to the studies of the adenosine A_2 receptor subtype. A series of recent reviews (Daval et al., 1996; Latini et al., 1996a,b; Ongini and Fredholm, 1996; Fredholm and Svenningsson, 1998) discusses the significance of of adenosine A_2 receptors in normal and pathologically altered functions of the brain, particularly in the process of slow neurodegeneration seen in diseases like Parkinson's or Huntington's type (Ferré et al., 1997). It is, therefore, rather surprising that despite the relevance of several effects evoked by adenosine A_2 receptors to the pathology of stroke, the knowledge of their involvement either in the generation or prevention of ischemic brain damage is very limited. The existing studies indicate that inhibition of adenosine A_{2A} receptors by selective antagonists reduces cerebral damage induced by global ischemia (Gao and Phillis, 1994; Phillis, 1995; von Lubitz et al., 1995a,b), while a slight improvement of postischemic cortical blood flow by a preischemically administered selective adenosine A_{2A} receptor agonist has no significant impact on neuronal surficial (von Lubitz et al., 1995a,b). The data on focal ischemia are even more limited, although reduction of the infarct volume has been demonstrated (Ongini et al., 1997).

In similarity to adenosine A_1 receptors, the neuroprotective effects of adenosine A_{2A} receptor antagonists consist, most likely, of several components that may involve reduction of neurotransmitter (particularly glutamate) release (Simpson et al., 1992), possible attenuation of ischemia-induced aberrations in adenosine A_{2A} receptor-mediated modulation of striatal dopamine D_2 receptors (von Lubitz et al., 1995a,b), and prevention of microglial activation, the latter process requiring a concordant activation of adenosine A_2 and A_1 receptors (Gebicke-Haerter et al., 1996, see also reviews by Schubert et al., 1994, 1997).

Cerebroprotection obtained with adenosine A_{2A} receptor antagonists provides a highly curious contrast to what is presently known about these receptors' role in regulation of neutrophils and reperfusion damage (Jordan et al., 1997). Neutrophil invasion beginning approximately 15 h after ischemia is a characteristic hallmark of the evolving cerebral infarct (Kalimo et al., 1997), and its primary task is the elimination of the neuronal debris. The process of neutrophil phagocytosis involves several highly toxic enzymes whose activity generates superoxide anions, hydrogen hydroxide, hydrochloric acid, and tumor necrosis factor α (TNF-α; Cronstein, 1997). Since extrusion of phagolysosome contents into the extracellular space results in destruction of the surrounding uninjured cells, it is believed that the intense activity of activated neutrophils is the main source of reperfusion injury (Grace, 1994; Zimmerman and Granger, 1994; Cavannagh et al., 1998). High concentration of adenosine stimulate neutrophil adhesion to the vascular endothelium (Cronstein et al., 1986; Nolte et al., 1992) and phagocytosis, while low levels inhibits both processes (Cronstein et al., 1986; Salmon and Cronstein, 1990; Becker et al., 1996).

Prevention of neutrophil degranulation (Bouma et al., 1997), and reduction of the concomitant release of TNF-α (Prabhakar et al., 1995; Thiel and Chouker, 1995) may have an important bearing on the amelioration of pathological changes induced by cerebral ischemia (Yamasaki et al., 1996). All these processes are induced either by elevation of extracellular adenosine, stimulation of adenosine A_2 receptors with adenosine analogues, or by exposure to adenosine A_2 receptor agonists (Cronstein, 1997). Yet, in all models of cerebral ischemia and stroke (Gao and Phillis, 1994; Phillis, 1995; von Lubitz et al., 1995a,b; Ongini et al., 1997) significant protection has been obtained only by the treatment with the antagonists, with the agonists promoted adverse outcome. The explanation of this apparent paradox may be found in the fact that in all studies of cerebral ischemia, the drugs (antagonists) were given prior to the insult. Hence, the treatment affected most likely only the initial segment of the entire pathophysiological complex, e.g., neurotransmitter release and excitotoxicity. Neutrophil-mediated phenomena (delayed, as noted above, by approximately 15 h), remained entirely unaffected by the drug (whose presence would induce neutrophil activation, resulting in a conceivable diminution of the therapeutic effect). There is thus a still unexplored possibility that late administration of the selective adenosine A_{2A} receptor agonist may significantly amplify antagonist-mediated protection by reducing the intensity of inflammatory processes at the late reperfusion stage.

Cerebral functions of adenosine A_{2B} receptors remain virtually unknown. It has been shown that this receptor subtype contributes to the accumulation of cAMP in primary astrocyte culture (Peakman and Hill, 1994), and mediates increase of interleukin-6 mRNA in human astroglioma cells (Fiebich et al., 1996). Their involvement in the functioning of mast cells may have an indirect effect on the brain through vascular phenomena, e.g., regulation of leukocyte adhesion (Suzuki et al., 1995; del Zoppo, 1997; Yong et al., 1997), or through mast cell participation in brain pathology, e.g., allergic encephalomyelitis (Dimitriadou et al., 1997; Rouleau et al., 1997). Recent reviews discuss extensively peripheral actions of adenosine A_{2B} receptors (Feokistov and Biaggioni, 1997; Feoklistov et al., 1998; Linden et al., 1998).

2.3.3. Adenosine A_3 receptors

Among the first described biological effects of adenosine A_3 receptor stimulation were degranulation of mast cells (Ramkumar et al., 1993; Fozard et al., 1996), and hypotension caused by the concomitant constriction of arterioles (Fozard et al., 1996). Thus, in similarity to adenosine A_{2B} receptor, adenosine A_3 receptor subtype may be involved in some aspects of cerebral blood flow

regulation, although, due to the latter's low affinity for adenosine (1 μM as opposed to 10–30 nM for either adenosine A_1 and A_2 receptors, respectively), its impact would be felt only under conditions that elevate extracellular adenosine concentration, e.g., seizures (Schrader et al., 1980; Winn et al., 1980; see also Lipper et al., 1994; Taboulet et al., 1995). Correspondingly, the decline of extracellular adenosine soon after ischemia indicates that adenosine A_3 receptors play only a minor (if any) role during postischemic reperfusion (Dirnagl et al., 1994; Kim et al., 1994; Hossman, 1997). Therefore, although von Lubitz et al. (1994) have shown that preischemic administration of a selective adenosine A_3 receptor agonist N^6-(3-iodobenzyl)-5′-(*N*-methylcarbamoyl) adenosine (IB-MECA) results in a significant delay in the return of postischemic blood flow, their findings do not indicate the involvement of adenosine A_3 receptor in regulation of the postischemic flow. More likely, the long lasting vasoconstrictive effect of the exogenously applied IB-MECA was responsible for the observed response.

Their effects on mast cells and vasoconstriction notwithstanding (Fozard et al., 1996), the biological role of adenosine A_3 receptors remains largely unclear. The concentration of adenosine A_3 receptors in the brain is 10–30 times lower than respective concentration of adenosine A_1 and A_2 receptors subtypes in the cortex and striatum. Moreover, both peripheral and central distribution of adenosine A_3 receptors varies among species (Jacobson et al., 1995; von Lubitz, 1997a,b), and the same is true of their pharmacological properties (Ji et al., 1994).

The combination of clinical use of adenosine in treatment of supraventricular tachycardia, large amount of available and convincing data on adenosine-mediated cardioprotection (reviewed by Mullane and Bullough, 1995; Cook and Karmazyn, 1996; Shryok and Belardinelli, 1997), and encouraging results with adenosine A_3 receptor agonists in prevention of cardiac ischemic damage (Hill et al., 1998; Liang and Jacobson, 1998) are probably among the chief reasons why most of the present work concentrated (and still concentrates) on cardiovascular functions of adenosine A_3 receptor, with the brain given only a very scant attention.

Available data indicate that adenosine A_3 receptors may play a very important role in generation of ischemic brain damage. Thus, it has been shown that activation of hippocampal adenosine A_3 receptors results in desensitization of adenosine A_1 receptor-mediated inhibition of excitatory synaptic transmission (Dunwiddie et al., 1997), while in CA3 neurons adenosine A_3 receptors potentiate calcium currents in a protein kinase A (PKA)-dependent manner that is characterized by a negative coupling to the Ca^{2+} current (Fleming and Mogul, 1997). Since PKA is one of the protein kinases severely affected by cerebral ischemia (Domanska-Janik, 1996; Tanaka et al., 1997), its functional derangement may contribute to the exacerbation of damage observed following preocclusive administration of the selective adenosine A_3 receptor agonist IB-MECA (von Lubitz et al., 1994). On the other hand, despite the demonstration that A_3 receptors participate in a sustained activation of phospholipase D (Ali et al., 1996) which necessary for neutrophil phagocytosis and generation of the oxidative bursts (Bonser et al., 1990; Serrander et al., 1996; Watson and Edwards, 1998), adenosine A_3 receptors are probably not involved in postischemic inflammatory processes as indicated by a powerful inhibitory effect of the selective agonist IB-MECA on degranulation of human neutrophils (Bouma et al., 1997). Moreover, activation of adenosine A_3 receptors inhibits both induction of TNFα gene and liberation of this cytokine in murine macrophages (McWhinney et al., 1996; Bowlin et al., 1997). Finally, adenosine A_3 receptors have been suggested to act as the regulators of differentiation and death in astrocytoma cells (Abbracchio et al., 1997a,b), with low (nM) concentrations promoting differentiation (Abbracchio et al., 1997a,b), and high (μM) inducing apoptosis. (Abbracchio et al., 1997a). Similar results were obtained in HL-60 and U-937 cell lines (Yao et al., 1997).

The beneficial results of A_3 receptor stimulation observed in vitro (and cardioprotection in vivo, see Auchampach et al., 1997) stand in a stark contrast to the diametrically opposed data obtained in studies of neurotoxicity in vitro (Sei et al., 1997), and cerebral ischemia in vivo (von Lubitz et al., 1994, von Lubitz et al., in press; von Lubitz, 1997a,b). Sei et al. (1997) have shown that, when given alone, only high concentrations of the selective adenosine A_3 receptor agonist Cl-IB-MECA are capable of inducing release of lactate dehydrogenase (LDH, a marker of cell death) from rat cerebellar granule cells. However, when the cells were exposed to non-toxic levels of glutamate (50 μM) followed by the addition of only 1 μM Cl-IB-MECA, LDH release increased almost twofold. Similarly, pretreatment of gerbils with IB-MECA prior to 10 min global ischemia resulted in a significant increase of postischemic morbidity and mortality (von Lubitz et al., 1994). On the other hand, chronic treatment with IB-MECA, and acute preischemic administration of the selective A_3 receptor antagonist 3-ethyl-5-benzyl-2-methyl-6-phenyl-4-phenylethynyl-1,4-(+/−)-dihydropyridine-3,5-dicarboxylate (MRS 1191) reversed these effects, and also resulted in a long lasting depression of nitric oxide synthase (NOS, von Lubitz, 1997a,b; von Lubitz et al., in press).

The widely divergent results of adenosine A_3 receptor stimulation in non-neuronal and neuronal systems indicate that the consequences of such stimulation are, most likely, drastically modified by the presence of NMDA receptors. As discussed above, ischemic activation of NMDA receptors results in adenosine liberation whose extracellular concentration rapidly reaches the level of at least 40 μM (e.g., Hagberg et al., 1987), i.e., more than sufficient for the optimal stimulation of adenosine A_3 receptors (Jacobson et al., 1995). Since activation of the latter has been shown to attenuate the efficacy of presynaptic inhibition

mediated by A_1 receptors (Dunwiddie et al., 1997), one may expect that the impaired modulation will promote sustained glutamate release and further stimulation of NMDA receptors. Activity of the latter will, in turn, lead to a continuous release of adenosine that will maintain its extracellular concentration at a sufficiently high level to ensure uninterrupted activation of adenosine A_3 receptors. Consequently, adenosine A_3 receptor-mediated attenuation of glutamate liberation will be enhanced even further, and the entire process will become self-fueling. In other words, it is very likely that ischemia transforms the process of adenosine-mediated egotropic inhibition that, under normoxic conditions, ensures the flexibility of synaptic responses (Brundege and Dunwiddie, 1996) into a self-sustaining process of egotropic excitation leading to the neuronal death.

Rapid induction of astrocyte apoptosis (Abbracchio et al., 1997a) by micromolar concentration of adenosine A_3 receptors indicates that ischemically increased concentration of extracellular adenosine will have an adverse, maybe even destructive, impact also on these cells (Glowinski et al., 1994). The contribution of adenosine A_3 receptors to ischemia-evoked failure of glutamate uptake (Pellerin and Magistretti, 1994; Longuemere and Swanson, 1995; Swanson et al., 1995b) and reversal of glutamate transporters (Mitani et al., 1994; Longuemere and Swanson, 1995) is unknown. However, the latter processes would provide a major source for further increase of the already elevated extracellular glutamate. Thus, the original aberration of adenosine A_1 receptor-mediated modulation of glutamate release triggered by the activation of A_3 receptors by the maximal increase of adenosine concentration, may trigger a chain reaction affecting not only neurons but the entire volume of the intensely ischemic tissue. Eventual loss of adenosine receptors either due to their desensitization or downregulation will finally interrupt the process.

Most likely, the inhibitory effects of adenosine A_1 receptors prevail during very mild ischemic episodes. Hence, transient ischemic attacks and other forms of mild ischemia do not result in perceptible damage. However, once the extracellular concentration of adenosine reaches and remains at the critical micromolar level either due to the duration of ischemia or to the sheer volume of the affected tissue, the damaging effects mediated by adenosine A_3 receptors will predominate.

Despite the vicious nature of the processes likely to be elicited by intraischemic stimulation of adenosine A_3 receptors, the actions that they mediate, i.e., vasoconstriction and promotion of tissue damage may, nonetheless, serve as an important part of the highly protective 'retaliatory metabolite' concept of adenosine proposed by Newby (1984). Viewed in this context, the principal role of A_3 receptors in ischemia would be to promote rapid isolation and elimination of the most intensely affected tissue by the combined effect of adenosine A_3 receptor-induced vasoconstriction (metabolic excision), and promotion of cell death (excitotoxic neuron and apoptotic astrocyte death or physical excision). These actions may assist in shifting the rapidly dwindling metabolic resources away from the most severely affected (i.e., irreversibly damaged) tissue to the penumbra zone, and enhance the latter's ability to survive the insult. Consequently, the sum of ischemia-evoked actions of adenosine A_3 receptors may serve as the 'last ditch' defence of the penumbra.

The discrepancies in the effects of selective adenosine A_3 receptor agonists against cerebral vs. cardiac ischemia where extensive protection by these drugs has been described (Stambaugh et al., 1997; Hill et al., 1998; Liang and Jacobson, 1998), gives ground to concerns in view of potential neurological complications of such treatment. Invariably, and independently of its etiology, even a mild cardiac arrest results in global cerebral ischemia. Neurological and neuropathological impairment is quite common, although its intensity depends on the duration of the arrest (Abramson et al., 1985; Horn and Schlote, 1992). Thus, while the preceding discussion of possible ischemic effects of adenosine A_3 receptor stimulation is largely speculative, the fact that preischemic stimulation of these receptors aggravates cerebral damage (von Lubitz et al., 1994) dictates caution in using adenosine A_3 receptor agonists to protect ischemic heart. Further studies are necessary to exclude the possibility of the latter treatment inadvertently inflicting additional damage on the already impaired brain especially that, in extreme cases, such treatment may exacerbate cerebral damage beyond the level of recovery.

3. Side effects of adenosine

3.1. Therapeutically beneficial effects

Even moderate hyperthermia has a profoundly adverse effect on the outcome of stroke, and elevation of body temperature by as little as 1°C increases the risk of poor outcome 2.2-fold (Reith et al., 1996). Numerous authors (Ginsberg et al., 1992; Maher and Hachinski, 1993; Kempski, 1994; Schwab et al., 1994; Lanier, 1995; Ginsberg and Busto, 1998; Meden et al., 1998) suggested hypothermia as means of reducing ischemic brain damage, and a large number of experimental animal studies (reviewed by Colbourne et al., 1997) amply confirm this conclusion. Moreover, emerging studies of hypothermic interventions in traumatic brain injury indicate the beneficial effect of lowered brain temperature (Clifton, 1995; Young-Su and Ishikawa, 1997).

Both peripheral and central exposure to adenosine receptor A_1 agonists results in a significant hypothermia (Anderson et al., 1994) consequent to the depression of energy metabolism (Kulinski et al., 1987; Anderson et al.,

1994; Zhong et al., 1998). However, Daval and Nicolas (1998) have shown that, at concentrations close to the receptor affinity constant, the depressant effect of adenosine on cerebral energy metabolism is, at best, minimal. Only when the concentration of extracellular adenosine is elevated during seizures or in the hypoxia/ischemia, the modulatory effect of adenosine on energy demand/supply becomes much more pronounced (Bruns, 1991).

Hypothermic effects of adenosine A_1 receptor activation are related in great part to their impact on the reduction of neurotransmitter release, and the concomitant depression of electrical activity responsible for at least 40% of the cerebral metabolism (Astrup et al., 1981). Studies involving metabolic mapping of cerebral metabolism confirm this conclusion, indicating that functional activity elevates metabolic rate predominantly within the terminal projection zone of the activated pathway (Sokoloff, 1993), i.e., within the area topographically corresponding to the predominant location of adenosine A_1 receptors (Deckert and Jorgensen, 1988).

Unquestionably, adenosine-induced depression of body/brain temperature is an important although indirect element of its therapeutic properties. Moreover, since hypothermia induces supersensitivity of adenosine receptors (Broadley et al., 1985), it is conceivable that the robustly neuroprotective effects of agonist stimulation of adenosine A_1 receptors that have been consistently reported by several authors (reviewed by Rudolphi et al., 1992; von Lubitz et al., 1995a,b; von Lubitz, 1997a) may be enhanced by the long lasting depression of body temperature induced by these drugs. In summary, despite the claims that neuroprotective impact of adenosine A_1 receptor agonists is consequent to their hypothermia-inducing properties (Miller and Hsu, 1992), it is more likely that the totality of the evoked effects (including hypothermia) is responsible for the beneficial outcome of pre- and postischemic administration of adenosine A_1 receptor agonists.

3.2. Therapeutically harmful effects

In a recent review, McCulloch (1996) stressed the importance of hypotension on the prognosis of recovery from stroke, and both experimental studies (Wahlgren et al., 1994; Zhu and Auer, 1995), and clinical trials (Squire et al., 1995) clearly indicate the relation between lowered blood pressure and the increased chances of poor outcome. Unfortunately, probably the most serious consequence of systemic administration of adenosine (and many of its analogues) is the significant depression of arterial blood pressure (Kassell et al., 1983; Stange et al., 1989; Park et al., 1991; White et al., 1996) induced by the activation of both adenosine A_1 and A_3 receptors. However, Bulley and Wittnich (1995) have shown that changes of both systolic and diastolic pressure are markedly affected by the dose and the rate of adenosine infusion. Hence, it is possible that a careful modification of the route of administration and dosing may alleviate hypotensive effects of adenosine. The results of preliminary experiments performed at our laboratory are encouraging.

3.3. Adenosine-based therapy of ischemic stroke

Since elevation of the extracellular adenosine concentration in stroke is both a site- and event-specific phenomenon, it opens a possibility for implementing adenosine-based interventions based on localized manipulation of adenosine receptors instead of a systemic administration of drugs targeted at specific receptors.

Recently, Picano and Abbracchio (1998) suggested that the clinical trials of platelet anti-aggregation therapy, in which the effects of acetylsalicylic acid and dipyridamole were investigated, serves as an example of adenosine-based therapy. Dipyridamole is a well-known platelet aggregation inhibitor whose administration prevents adenosine uptake, and results in a significant elevation of adenosine blood concentration independently of the mode of its administration (Dresse et al., 1982; Wang et al., 1992; Hegedus et al., 1997). When given at 0.7 mg kg^{-1} i.v., dipyridamole inhibits adenosine uptake in rabbits by 25%, although the effect is rather short-lasting (Hegedus et al., 1997). In dogs, a 2.2-fold adenosine increase has been reported (Wang et al., 1992). Dipyridamole had no effect either during or immediately following brain ischemia, although increased presence of adenosine was seen at 15 min postischemia (Park and Gidday, 1990).

The results of the European Stroke Prevention Study showed that both salicylic acid and dipyridamole were effective in reducing the incidence of ischemic stroke and transient ischemic attacks (Diener et al., 1996; Forbes, 1997). However, although it is very tempting to believe that adenosine-related cerebrovascular and neuroprotective effects of the administered dipyridamole played a significant role in the beneficent outcome of the platelet anti-aggregation trials, the belief may be premature.

As discussed in the preceding section, adenosine receptors desensitize rapidly. Moreover, several animal studies (reviewed by Jacobson et al., 1996) have clearly shown that chronic administration of even modest doses of either agonists or antagonists of all three adenosine receptors induce desensitization resulting in a dramatic reversal of the therapeutic effect present during acute stimulation.

While the cerebral neurons can only age and disappear, and the turnover of the vascular endothelium in normal tissues is rather slow (Hobson and Denkamp, 1984), the turnover of platelets is on the other hand, a comparatively fast phenomenon (Mustard et al., 1966; Cunietti et al., 1981; Smith, 1995). Hence, there is a continuously high chance that, at any given time, the number of platelets with their receptors not yet downregulated by dipyridamole is significant, and that a daily dose of dipyridamole will

sustain the antiaggregatory effect. Neurons, on the other hand, (and probably endothelium as well) will, most likely, be less fortunate, and downregulation of their receptors will result in the loss of the primarily A_1 receptor-maintained neuroprotective mechanisms. Again, further experimental work is needed since studies of dipyridamole-induced neuroprotection in vitro (Lobner and Choi, 1994; Farinelli et al., 1998) are inconsistent. Although an extensive literature search failed to revel any papers describing the effect of dipyridamole on the outcome of cerebral ischemia in vivo (but see Hegedus et al., 1993), a study of in which another adenosine uptake inhibitor, nitrobenzylthioadenosine (NBT1), was administered directly into the brain via a dialysis probe showed a significant reduction of postischemic hypoperfusion (Gidday et al., 1996).

Adenosine kinase inhibitors offer a very direct approach to the local elevation of extracellular adenosine concentration. At least two groups (Miller et al., 1996; Jiang et al., 1997) showed that treatment of rats with 5′-deoxy-5-iodotubercidin (5′d-5IT) administered either pre- and postischemia (Miller et al., 1996; Jiang et al., 1997) or postischemia (Miller et al., 1996) resulted in a significant decrease of the infarct volume in the rat model of focal ischemia. Critical studies of postischemic administration are still to be published.

Enhancement of adenosine A_1 receptor binding properties provides another venue, and Gidday et al. (1996) and Halle et al. (1997) have demonstrated neuroprotection in the unilateral model of cerebral ischemia induced by ligation of one carotid artery and hypoxia. Studies using more 'classical' methods based on direct (systemic) treatment with adenosine A_1 receptor agonists, most of which demonstrate robust attenuation of cerebral damage following both global and focal ischemia, have been extensively discussed in a series of recent reviews (Rudolphi et al., 1992; von Lubitz et al., 1995a,b; Sweeney, 1997; von Lubitz, 1997a).

Despite the rapid loss of adenosine A_1 receptors, the therapeutic window for treatment with either with adenosine uptake or degradation inhibitors, or agonists of this receptor may be longer than previously assumed. Bischofberger et al. (1997) have shown a significant reduction of the neuronal loss in gerbils exposed to 10 min global ischemia followed by treatment with adenosine amine congener (ADAC) as late as 12 h postischemia. Importantly, ADAC had no acute cardiovascular side effects at the therapeutic dose (100 $\mu g\ kg^{-1}$, i.p.), although at higher amounts ($\geq 400\ \mu g\ kg^{-1}$) the drug induced rapid decline of the mean arterial blood pressure. The neuroprotective effects of ADAC were most likely related to its ability to reduce glutamate release (Boyd et al., 1996). Investigators at Novo Nordisk have also reported a new selective adenosine A_1 receptor agonist (NNC 21-0041) characterized by an equally mild cardiovascular profile (Knutsen et al., 1995). The drug has powerful anticonvulsant and neuroprotective properties, even when administered at very low doses (Sheardown et al., 1994, and unpublished observations).

Very little is known about the cerebral effect of adenosine A_3 receptor acting drugs. von Lubitz et al. (1994, von Lubitz et al. (in press) have shown that acute treatment of global ischemia with the A_3 agonist IB-MECA results in a very substantial aggravation of neuronal damage, while its chronic application is powerfully neuroprotective. Postischemic treatment with the antagonist MRS 1191 reproduced the effect of chronic treatment (von Lubitz, 1997b), indicating that adenosine A_3 receptors are subject to desensitization (downregulation) in vivo (see Jacobson et al., 1996), as well as in vitro (Palmer and Stiles, 1995; Palmer and Stiles, 1998).

Propentofylline [HWA 285; 1-(5′-oxyhexyl)-3-methyl-7-propylxanthine] has been the subject of several studies, consistently inducing neuroprotection in both global and focal ischemia models. (DeLeo et al., 1987; Dux et al., 1990; Miyashita et al., 1992; Park and Rudolphi, 1994; Matsumoto et al., 1996). The drug acts as a moderately efficient inhibitor of adenosine uptake (Fredholm and Lindström, 1986; Fredholm et al., 1994b), and as weak adenosine A_1 receptor antagonist whose potency at adenosine A_1 is higher than adenosine A_2 receptor (Fredholm et al., 1994a,b). Rather curiously, in view of its antagonism of adenosine A_1 receptors, propentofylline reduced postischemic release of glutamate in gerbils (Miyashita et al., 1992) and rats (Andine et al., 1990). Most likely, the reduction was related to propentofylline-induced elevation of extracellular adenosine concentration reported by Andine et al. (1990). Inhibition of microglial activation (reviewed by Parkinson et al., 1994; Schubert et al., 1997), and stimulation of nerve growth factor (N.F.) release from astrocytes (Shinoda et al., 1990) have been also reported.

Whether the success of recently conducted limited-scope clinical trials of propentofylline against vascular and Alzheimer type dementia (Rother et al., 1996; Kittner et al., 1997) may indicate that the manufacturer will consider its testing against ischemic disorders remains to be seen.

4. Conclusions

Despite a large number of studies clearly indicating powerful cerebroprotective effect of adenosine receptor stimulation, it is too early to say whether adenosine-based therapies will find their way to the hospitals as a treatment of ischemic stroke. Despite vigorous studies, many aspects of the mechanisms involved in adenosine-mediated protection of ischemic brain are still unclear. On the other hand, new drugs with a continuously increasing selectivity and improved cardiovascular profile begin to emerge. Hence, there is a possibility that even the gravest doubts about adenosinergic treatment, particularly that of seemingly unavoidably induced hypotension, may, eventually, be put to rest. Thus, while there is no doubt that the concept of adenosine receptor-based therapy is alive and rather quite

well, there is equally little doubt that much work needs to be done before adenosine receptor acting compounds will become a standard part of the neurological armoury. As for the question 'Shall we or shall we not?', the answer is: 'we do not know yet'.

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