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Adenosine: a Prototherapeutic Concept in Neurodegeneration

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ADENOSINE AND BRAIN: THE VIEWS AND THE VISTAS

Ten years ago, Newby introduced a new description of adenosine: “the retaliatory metabolite.”[1] The theoretical notion that adenosine may protect against tissue injury[2] evolved rapidly into a practical demonstration of powerful neuroprotective effects of endogenous adenosine and its analogues.[3–5] Subsequent improvement in understanding both the effects of adenosine receptor stimulation and the pathological processes that accompany numerous neurological disorders ultimately led to proposals that adenosine-based therapies may be effective not only in stroke and seizures, but also in Alzheimer's, Huntington's and Parkinson's diseases, and a number of psychiatric pathologies.[5,6]

ADENOSINE AND BRAIN: THE FUNCTIONS

Endogenous Brain Adenosine and Pathologic Stress

Technical difficulties complicate the exact measurement of extracellular brain adenosine concentration.[4] Currently, the level of free adenosine level in the interstitial brain space of unanesthetized, freely moving animals is estimated at 50–300 nM.[4] More importantly, however, several laboratories have consistently reported that the amount of extracellular adenosine increases dramatically following cerebral metabolic stress caused by seizures, hypoxia, or ischemia.[4]

In focal ischemia (and probably global as well), the reduction of cerebral blood flow (CBF) correlates with the concomitant elevation of both adenosine and glutamate.[7] However, while increased release of adenosine occurs at CBF values of 25 ml/100 g/min, further reduction ofCBF (20 ml/100 g/min) is necessary to elevate concentration of the extracellular glutamate. Quite recently, Hoehn and White[8,9] showed that release of excitatory amino acids elicited by electrical field stimulation also results in the release of adenosine—an effect mediated in part by both *N*-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid (AMPA) receptors. It appears, therefore, that glutamate-mediated hyperexcitation of neurons (such as seen in cerebral ischemia) may provide an additional, and somewhat unexpected, stimulus for further increase in adenosine release. These observations indicate that, in view of the powerful inhibitory effect of adenosine on the release of several excitatory neurotransmitters (see below), it is quite likely that increase in the concentration of interstitial adenosine, which both precedes and accompanies massive intraischemic release of glutamate,[10–13] constitutes part of a mechanism whose operation provides a transient, endogenous protection of the brain against injury.[5]

Cerebral Receptors of Adenosine

Endogenous adenosine acts at three principal G-protein-associated receptor subtypes: A_1, A_2 and A_3.[14,15] Both the molecular structure and the nature of the effector coupling are known for all three subtypes.[16,17] Cerebral A_1 receptors are linked to several second messenger systems, and one of their characteristic responses to stimulation is inhibition of adenylate cyclase.[14] Activation of A_2 receptors stimulates adenylate cyclase,[14] whereas activation of A_3 receptors inhibits it, and also stimulates phosphoinositide metabolism.[18] Although their specific distribution varies,[19] all three adenosine receptor subtypes are found in the brain.[15,20] A_1 receptors are predominantly found in the hippocampus, IV–VI laminas of the cortex, striatum, amygdala, and superior colliculus, and appear to be codistributed with NMDA receptors,[21,22]

A_2 receptors, of which two subclasses (A_{2a} and A_{2b}) exist, abound on smooth muscle and endothelial cells of cerebral blood vessels, where they mediate vascular effects of adenosine.[23] High-affinity A_{2a} receptors are particularly well represented in the striatum and other dopamine-rich regions of the brain,[19] where they are colocalized with dopamine D_2 receptors, and exert profound modulatory effect on dopaminergic transmission.[24] Adenosine receptors on glial cells helong, most likely, to the low-affinity A_{2b} subclass.[4] Cerebral distribution of A_1 and A_2 receptors follows an intriguing pattern, *i.e.*, A_2 appear to be less abundant within regions where the density of A_1 sites is elevated, and vice versa. Differences in the anatomical distribution of A_1 and A_2 receptors may have striking behavioral consequences.[25] A_3 receptors are found throughout the brain but their density is much lower than that of either A_1 or A_2.[20] The cell type on which they are located is unknown.

Physiological Effects of Adenosine Receptor Stimulation

The principal function of adenosine in the brain is that of an inhibitory neuromodulator,[26,27] The inhibitory effects of adenosine are mediated mainly via both pre- and postsynaptic A_1 receptors.

Activation of presynaptic A_1 sites inhibits neuronal calcium uptake[28-30] and results in reduced release of several neurotransmitters, *e.g.,* acetylcholine, noradrenaline, dopamine, serotonin, and glutamate.[31–34]

Stimulation of both pre- and postsynaptic A_1 receptors causes activation of potassium[35–37] and chloride[38] conductances. The resultant elevation of the membrane potential and the depression of the membrane resistance[35,39] decrease neuronal excitability and firing rate.[35,40,41]

Apart from the involvement of adenosine A_2 receptors in regulation of CBF[23] adenosine A^2 receptors are responsible for accumulation of cyclic adenosine monophosphate (cAMP) in the brain.[4] The details of A_2 receptor involvement in neuronal physiology are still poorly understood, although existing evidence indicates that excitatory A_2 receptors are present in the hippocampus$_{42}$ and may be involved in potentiation of calcium-dependent neurotransmitter release[43,44] and in modulation of electrically evoked release of gamma-aminobutyric acid (GABA) in globus pallidus.[45] It is also known that in the striatum, A_2 receptors mediate control of gene expression in enkephalinergic neurons,[46] and that A_2 activation attenuates activity of the colocalized dopamine D_2 receptors through reduction of their affinity for D_2 agonists.[25,47,48] Finally, participation of A_2 receptors in generation of astrocytic edema has been also suggested.[49]

ADENOSINE AND NEUROPROTECTION: THE THEORETICALS

The first experimental confirmation of neuroprotective properties of adenosine analogues in cerebral ischemia has been provided by Evans *et al.*[52] and von Lubitz *et al.*[53,54] A variety of *in vitro* and *in vivo* models of hypoxic/ischemic models of neuronal injury have been used in most of the subsequent studies of neuroprotection afforded by adenosine, its analogues, and inhibitors of its uptake.[4] Moreover, the effect of these approaches has been also investigated in seizures[55] and in either clinical[56] or *in vitro* hypoglycemia.[57] Since pathophysiology of cerebral ischemia has been extensively reviewed,[58–60] for the purpose of the present review suffice to say that the arrest of brain blood supply results in a rapid depolarization of neuronal membranes,[61] massive release of excitatory neurotransmitters[11] and excitation of postsynaptic glutamate receptors (NMDA and non-NMDA[59]), followed by influx of calcium and its release from intracellular stores.[62] The latter process triggers a series of cascading events[60] that ultimately lead to neuronal demise.

From the preceding brief discussion of the effects of adenosine receptor stimulation it is apparent that adenosine analogues may be applicable in interrupting several iscfiemia-associated events, *e.g.,* membrane (hypoxic) depolarization, neurotransmitter release, hyperexcitation of NMDA receptors, and calcium influx.

Endogenous Adenosine and Hypoxic Depolarization

Rapid depolarization of neuronal membrane is one of the initial events evoked by either impaired or entirely interrupted supply of the cerebral blood flow.[63] Moreover, duration of hypoxic depolarization may be the determining factor that dictates the subsequent fate of neurons, *i.e.,* their survival or death.[64]

Hypoxic depolarization is associated with enhanced influx of calcium through voltage-gated calcium channels,[59] and concomitant increase in neurotransmitter release. Since intraischemic liberation of endogenous adenosine precedes that of glutamate,[7] and since intraischemically released adenosme both significantly delays the onset of hypoxic depoiarization[65] and reduces glutamate release,[66] it appears that adenosine-mediated protective processes take place already at the very beginning of the insult.

Adenosine A_1 Receptors and Excitatory Neurotransmitter Release

Significant reduction of intraischemic release of glutamate by the A_1 receptor agonist N^6-cyclopentyladenosine (CPA) and the A_1/A_2 agonist *N*-ethylcarboxamidoadenosine (NECA) has been demonstrated in the 4-vessel occlusion rat model of ischemia.[66] Reduction of glutamate release by the A_1 agonist N^6-cyclohexyladenosine (CHA) has been also reported in focal ischemia in the rat[3] and in forebrain ischemia in the gerbil (Marangos and von Luhitz, unpublished). However, while glycine levels were significantly attenuated by CRA in a study of global ischemia in rahhits,[67] the reduction of glutamate showed only a dose-dependent but statistically insignificant trend. Nonetheless, even if in the latter study glutamate release was affected only to a limited extent, the protective effect of adenosine agonist is still likely.

Glycine is necessary for activation of the ion-gated channel of the NMDA receptor which regulates calcium influx.[68] Moreover, several studies have showed that glycine antagonists and partial agonists have a neuroprotective effect.[69,70] Therefore, It is conceivable that, despite a variable effect on the liberation of glutamate, CHA-mediated reduction in glycine release may diminish the functional efficiency of the NMDA receptor-associated ion-gated channel, and thereby decrease the subsequent calcium overload.

Endogenous Adenosine and Glutamate Uptake Sites

Postischemic release of glutamate is comparatively brief and abates within approximately 30 min.[11] However, postischemic depression of CBF seen severe ischemia (hypo perfusion stage) may result in secondary hypoxia,[71] Hence, a supplementary elevation in the extracellular glutamate concentration is also quite possible and may, unless astrocytic transport mechanisms remain intact, lead to exacerbation of the excitotoxic processes initiated by the primary event. Interestingly, Anderson *et al.*[72] have showed that even a brief (5-min) ischemia results in a prolonged upregulation of high-affinity excitatory amino acid (EAA) transport sites. At the same time, Schmidt *et al.*[73] have showed that a brief 10-min exposure to adenosine produces a significant increase in the density of high-affinity glutamate and aspartate uptake sites in rat hippocampal slices. Therefore, it is possible that intraischemic elevation of brain adenosine[74] may, apart from its effect on neurotransmitter release, also result in a sustained upregulation of EAA transport ers. Consequently, due to its control of both release and uptake of EAAs, endogenous adenosine may play an important role in prevention of excitotoxic damage following very brief ischemic periods, the absence of which has been noted by several authors.[75,76]

Postsynaptic Effects of Adenosine and Neurodegeneration

The intensity of excitatory synaptic input depends on the amount of NMDA-mediated influx of Ca^{2+}[77] which, in turn, increases membrane depolarization and acts as a synaptic amplifier. Since the evoked influx of calcium is tightly controlled by postsynaptic A_1 receptors even at low extracellular Ca^{2+} concentrations,[29,30,78] such control tends to attenuate calcium-mediated synaptic amplification.[4] Consequently, adenosine and its postsynaptic A_1 receptors regulate critical input frequencies required to operate postsynaptic NMDA receptors, as was recently demonstrated by Schubert and his colleagues.[30,79]

The additional, albeit indirect, benefit of reduced NMDA receptor-mediated depolarization elicited by interaction of adenosine with its A_1 receptors is the effect on voltage-sensitive K^+ currents.[35] DepolarizatIOn appears to block these currents and enhances neuronal excitability and firing rate.[80] Hence, vigorous activatIOn of A_1 receptors by elevated concentrations of extracellular adenosine may counteract NMDA receptor-mediated depolarization, and drive the membrane potential toward voltage ranges at which depolarization-dependent block of potassium conductance is either less likely or does not occur.[4]

Apart from its enhancing effect on potassium conductance,[36,37,81] adenosine stimulates voltage-dependent Cl^- conductance as well.[38,82] It has been suggested that the openmg of this conductance may diminish accumulation of intraneuronal Cl^- during repetitive firing[4] which, unless prevented, will eventually impair GABAergic inhibition.[83] Elevation in extracellular adenosine during periods of enhanced neuronal activity[41] may, therefore, assist in maintaining GABA-mediated inhibition, and constitute another functional aspect of the protective adenosine/adenosine receptor complex.

Adenosine A_2 Receptors and Neurodegeneration

The concept of A_2 receptor involvement in neurodegeneration has not been pursued with the same vigor as that of A_1 receptors. There is, however, indirect, evidence that A_2 receptors may play a pivotal role in neuronal death observed in the striatum, and possibly also in the substantia nigra. Contrary to general belief, it is the dorsolateral aspect of striatum rather than the hippocampal CA4 sector[75] that appears to be endowed with the highest sensitivity to ischemic insult.[84,85] Light microscopic evidence of neuronal impairment in the striatum is clearly discernible already 1 h after a very light ischemic episode. while acute ischemic damage in the hippocampal CA4 appears 6–12 h after the event.[84] Rapid, intraischemic

release of dopamine and glutamate,[85,86] persistent elevation of cAMP,[87] and eventual loss of dopamine D_2 receptors[86] precede morphologic damage of striatal neurons.

Globus *et al.*[85] have showed that, while increased concentration of intrastriatal dopamine alone has no adverse effect, elevated concentration of both dopamine and glutamate is associated with striatal vulnerability to ischemia. Since dopamine D_2 receptors attenuate the effect of glutamatergic stimulation,[88] it is possible that accelerated postischemic loss of D_2 receptors, rather than elevated concentration of both qeurotransmitters per se may constitute one of the critical factors resulting in the apparent potentiation of glutamate-evoked damage. The most characteristic aspect of this damage is its containment to the medium-sized spiny neurons containing enkephalin and substance P,[84] *i.e.,* neurons receiving glutamatergic input from both substantia nigra and neocortex.[88] Moreover, the same medium-sized GABAergic enkephalin-containing neurons are also characterized by the highest density of adenosine A_2 receptors.[24]

Based on the existing evidence, and on the fact that stimulation of adenosine A_2 receptor decreases the affinity of D_2 receptors to agonist stimulation,[48] it is possible to construct a chain of conjectural events that may ultimately lead to the selective neuronal loss in the striatum. Most likely, the initial intraischemic surge of adenosine agitates high-affinity A_{2a} receptors located on enkephalin-containing GABAergic neurons. At the same time, the colocahzed D_2 receptors which attenuate glutamatergic excitation supplied by cortical and nigro-striatal fibers[88] will be stimulated by dopamine, whose concentration also increases. However, the activated A_2 receptors decrease affinity of the colocalized D_2 sites to dopamine,[24] thereby diminishing the efficiency of their counterexcitatory effect. Ultimately, combination of A_2-D_2 interactions and postischemic loss of D_2 receptors[86] will result in a progressive shift toward unopposed glutamatergic hyperexcitation whose intensity will, eventually, attain the level sufficient to induce excitotoxic damage of enkephalin-containing GABAergic neurons.

Contrary to A_1 receptors, the time course of ischemia-induced adenosine A_2 receptor disappearance is unknown. However, cerebral ischemia causes elevation in striatal cAMP that persists for at least 4 h after the reperfusion.[87] Since stimulation of A_2 receptors leads to production of cAMP,[4,14] its prolonged postischemic presence may indicate that the functional A_2 receptors are preserved for several hours following the insult. Moreover, it was shown recently that A_2 receptor stimulation enhances ischemia-evoked release of glutamate and aspartate.[44] Thus, although the mechanism involved in this process is unknown, the sustained operation of A_2 receptors may amplify the damage to enkephalin-containing GABAergic neurons even further.

Allowing that this speculative sequence of events is correct, its repercussions on “downstream” damage caused by ischemia may be significant. Both global and prolonged forebrain ischemia cause damage in the substantia nigra as well as in the striatum and the hippocampus.[89,90] Hence, possible involvement of A_2 receptors in development of the rapid damage to the inhibitory enkephalin-containing neurons in the striatum may contribute to the subsequent loss of inhibitory input to the substantia nigra, and amplify the adverse effects of ischemia-associated hyperstimulation also in that region.

The pattern of striatal neuron loss in cerebral ischemia is very similar to that observed in Huntington's chorea[84] and, although the postischemic fate of A_2 receptors is presently unknown, a significant decrease in their density was observed in striatal tissue of patients with Huntington's disease,[91] Since adenosine A_2 receptors appear to play an important role in pathophysiology basal ganglia associated with Huntington's and Parkinson's diseases,[25,46,92] drugs acting at these receptors may prove very useful in the treatment of

these disorders. Involvement of A_2 receptors in neurodegenerative processes of different etiology is the subject of current, intensive studies at our laboratory.

Striatum apart, stimulation of adenosine A_2 receptors may result in an improved postischemic survival of neurons in other regions through, *e.g.,* improvement of postischemic CBF[93] or prevention of postischemic inflammatory processes.[94] Normalization of postischemic CBF may be obtained through A_2 receptor-mediated vasodilation[5,23,95] and through antithrombotic effects.[96,97] Moreover, since stimulation of A_2 receptors prevents activation of neutrophils, it may, through concomitant reduction in free radical release, diminish the damage to the endothelial lining of cerebral blood vessels.[98] Finally, stimulation of leukocyte A_2 receptors decreases their adherence to capillary walls, and appears to be involved in prevent ing postischemic "plugging" of cerebral capillaries.[99]

ADENOSINE AND NEUROPROTECTION: THE PRACTICALS

Effects of Acute Administration

The results of experimental studies of the neuroprotective effects of adenosine, its analogues, and agents affecting its turnover are the subject of several recent reviews.[3–5,100,101] Most of those studies concentrate on investigations of either forebrain or global cerebral ischemia, and use survival and/or neuropathology as the measures of outcome.

Due to their well-known physiological properties and their relevance in treatment of cerebral ischemia, A_1 receptors are the chief subject of the existing experimental work.[3,4] Significant neuroprotection has been reported in virtually all studies of focal (but see Roussel *et al,* 1991), global, and forebrain ischemia in which A_1 receptor agonists have been administered either shortly before or after the insult, whose duration ranged from 5 to 30 min.[3,4] However, since the maximum interval between pretreatment and ischemia was 15 min, and maximum postischemic delay did not exceed 30 min, the dimension of the therapeutic window within which acutely administered adenosine agonists are effective is uncertain. It is known, however, that rapid downregulation of A_1 receptors follows even a mild anoxic or ischemic episode,[103,104] and that 14–24 h after ischemia, A_1 receptors become dysfunctional.[4] Thus, since the strength of adenosine modulation depends on the density of A_1 receptors,[105] the therapeutic window for administration of A_1 analogues is probably not an extensive one.[4]

The veracity of neuroprotective effects of A_1 receptor agonists has been confirmed by studies in which A_1 antagonists have been used.[4] Uniformly, administration of antagonists has resulted in severe exacerbation of mortality,[106] and in amplified neuronal destruction.[4]

Contrary to the effects of A_1 receptor agonists, the results following acute administration of agents active at A_2 receptors is virtually unknown. Recently, however, Gao and Phillis[107] showed that pretreatment with a weakly selective A_2 antagonist CGS 15943 resulted in protection of the hippocampus against ischemic damage.Our own results (von Lubitz *et al.,* in preparation) indicate that A_2 antagonists administered prior to 10-min ischemia protect not only hippocampus but striatum as well.

Presently, only one report describes the effect of acute A_3 receptor stimulation on the outcome offorebrain ischemia,[50] The study shows that preischemic administration of a small dose (100 μg/kg) of a selective A_3 agonist, N^6 – (3-iodobenzyl)-adenosine-5′-methylcarboxamide (IB-MECA), results in an extensive hippocampal damage and a very high mortality (90%) within the initial 24 h after ischemia.

Despite their neuroprotective efficacy, the acute treatment with adenosine A_1 agonists is accompanied by two major side effects, *i.e.,* hypothermia and hypotension. Since hypothermia results in a significant reduction of postischemic neuronal damage,[107] it is possible that A_1 agonists mediate their neutron-sparing effect chiefly through the depression of brain temperature. However, both *in vitro* sutdies[108] and studies in which brain temperature has been carefully maintained[106] indicate that the protective effect is preserved also in the normothermic environment. Moreover, it must be remembered that, in the context of therapies aimed at stroke and brain ischemia, the comparatively mild hypothermic impact of A_1 receptor agonists may constitute a benefit rather than a hindrance.

Failure of cerebral perfusion pressure after ischemia is among the most critical factors that influence clinical recovery,[109,110] and hypotension and cardiodepression accompanying administration of A_1 agonists constitute potentially serious side effects of A_1 receptor-based therapies. Cardiovascular side effects of A_1 receptor agomsts may be countered by coadministration of peripheral adenosine antagonists. However, von Lubitz and Marangos[111] have showed that, although concomitant postischemic administration of the A_1 receptor agonist CHA and the peripheral adenosine antagonist 8-ᵖ-sulphophenyladenosine (8-SPT) in gerbils resulted in a full normalization of CHA-evoked hypotension, the combined CHA/8-SPT treatment does not improve either survival and neurological impairment scores beyond those attained with CHA alone.

Effects of Chronic Administration

Among all disorders for which adenosine-based therapies have been envisated, only stroke offers a target for their acute administration while most, if not all, other central nervous system (CNS) diseases require chronic, frequently even life-long, exposure. However, very little is known about the chronic effects of agents acting at adenosine receptors in the context of neuronal pathologies. The pioneering study of Rudolphi *et al.*[112] showed that chronic treatment with caffeine—a nonspecific A_1/A_2 antagonist—resulted in protection against ischemic damage in gerbils (*i.e.,* the exactly opposite effect to that obtained with acute administration of another nonspecific antagonist, theophylline),[76] Von Lubitz *et al.*[106,112,113,115] have investigated the consequences of chronic administration of drugs acting at adenosine receptors further, and have used the highly potent A_1 agonist CPA or antagonist 8-cyclopentyl-1,3-dipropylxanthine (CPX). The work of the latter authors has confirmed the results of Rudolphi and his colleagues,[76,112] and has also showed that while acute treatment with a selective A_1 receptor agonist is highly protectlve, chronic treatment with the same drug has a profoundly aggravating effect in several measures of postischemic recovery, *i.e.,* survival, neurological status, and preservation of ischemia-vulnerable brain regions. Treatment with A_1 receptor antagonists, on the other hand, produced a diametrically opposite effect, *I.e.,* acute administration enhanced, and chronic administration protected against the damage.[106] The same authors also showed that while acute treatment with adenosine A_3 receptor agonist enhanced ischemia-associated damage, chronic treatment was highly ameliorative,[50] Preliminary studies with agents acting at A_2 receptors indicate the same pattern of regimen-dependent reversal. Interestingly, regimen-dependency of the therapeutic outcome of adenosine-based treatment has been also described in NMDA-evoked seizures,[50,113,116] and in the water maze modd of learning and memory.[114]

ADENOSINE AND NEUROPROTECTION: THE PUZZLES AND THE PARADOXICALS

Despite numerous and convincing demonstrations of neuroprotective effects of endogenous adenosine, and despite highly alluring results of experimental treatment of cerebral ischemia with agents acting at all three adenosine receptor subtypes, a number of unsolved puzzles

exists. We have already mentioned the fact that, although critical from the therapeutic point of view, time limits for efficient administration of acute adenosine therapies in stroke and cerebral ischemia are unknown. Glial response to the activation of their A_1 and A_2 receptors is also very poorly known, although there are indications that both glycogenolysis[117] and astrocytic edema[118] may ensue.

Degradation of endogenous adenosine contributes to the generation of highly destructive free radicals.[119] Since administration of free radical scavengers virtually, eliminated production of superoxide species during and after cerebral ischemia,[119] therapies based upon elevation of endogenous adenosine may be less effective than those employing stimulation of adenosine receptors with appropriate analogues. Unquestionably, the problem requires a detailed and urgent examination. Finally, there is virtually no information on the interplay of individual adenosine receptor subtypes, although there are indications that such interplay may be critical for neuronal function and survival.[50]

The paradoxical effects of adenosine receptor-based therapies require further studies as well. The regimen-dependent nature of the outcome has been already mentioned. Prolonged stimulation by agonists or blockade by antagonists both *in vitro* and *in vivo* produces, respectively, either down- or upregulation of adenosine receptor density.[18,49,120] However, in some studies, no changes of either receptor density or ligand binding properties (K_d) were observed during prolonged exposure to selective A_1 agonists and antagonists, and to a nonselective A_1/A_2 angatonist theophylline *in vivo*.[106,115,116] On the other hand, Fastbom and Fredholm have showed that prolonged exposure to theophylline upregulates adenosine receptors, and Shi *et al.*[122] have reported that chronic treatment with caffeine (a nonspecific A_1/A_2 antagonist) both upregulates A_1 receptors and results in very dramatic density shifts of some receptor types (*e.g.,* GABA, dopamine, noradrenaline), while having no effect on others (*e.g.,* NMDA). Finally, chronic caffeine-mediated upreguiation of A_1 sites and its functional consequences were the most likely source of protection against ischemia reported by Rudolphi *et al.*[112]

Although the protective effect of chronically administered A_1 antagonists is easily explained when accompanied by receptor upregulation, the nature of the mechanisms behind ameliorative actions of a chronic antagonist regimen observed in absence of increased density of A_1 receptors remains entirely obscure. Changes in G-protein-mediated receptor-efIector coupling have been proposed as a putative answer to the regimen-dependent shifts seen after chronic exposure to both nonselective and selective agonists and antagonists[106,115,116] Significant alterations in $G_{S\alpha}$ and $G_{I\alpha}$ proteins that were unaccompanied by a corresponding change in their mRNAs have been seen in rat adipocytes following chronic treatment with A_1 receptor antagonist.[123] However, whether similar phenomena take place in the brain remains to be demonstrated.

The effect of acute stimulation of A_1 and A_3 receptors offers another paradox. While both receptors arc negatively coupled to adenylate cyclase (*i.e.,* reduce its levels), acute preischemic activation of A_1 causes extensive neuroprotection. Acute activation of A_3 receptors, on the other hand, has an equally extensive but damaging result in cerebral ischemia,[50] although it is protective against NMDA-evoked seizures.[51] Moreover, chronic administration of A_3 receptor agonist protects equally well against cerebral ischemia and against chemically and electrically evoked seizures.[50,51]

Clearly, there are a number of questions that require additional, extensive studies. On the other hand, even if several aspects of adenosine action on a living cell, be it a neuron, a cardiac myocyte, or a nephron are unknown, Newby's “retaliatory metabolite” has already found its practical application in cardiology. Thus, under the name “Adenocard™,”

adenosine is now clinically used in treatment of supraventricular tachycardias, and it is not a premature hope that soon the concept of adenosine-based therapies will also find its application in treatment of the disorders of the brain.

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