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REVIEW ARTICLE

ADENOSINERGIC SYSTEM AS AN ENDOGENOUS ANTICONVULSANT MECHANISM

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Abstract: The treatment of epilepsies remains far from adequate primarily due to inadequate understanding of the pathophysiology of seizures. The conventional approach for research into epilepsy has been study of factors responsible for initiation of seizures. However, now attention is being drawn to the spontaneous and abrupt arrest of seizures which suggests a distinct possibility of activation of an endogenous anticonvulsant mechanism(s), which may be targeted in future for controlling seizures. Of the various endogenous anticonvulsant mechanisms, the concept of an endogenous anticonvulsant substance has gained much experimental support and, many potential candidates have been postulated. Of these adenosinergic system appears to be the most promising. This review discusses the possible role of adenosinergic system in seizures, in relation to the available antiepileptic drugs and its therapeutic implications.

Key words : adenosinergic system, endogenous anticonvulsant substance (s), antiepileptic drugs, seizures, adenosine, adenosine receptors

Over the past two decades, several new antiepileptic drugs have been introduced worldwide. These include gabapentin, felbamate, lamotrigine, vigabatrin and oxcarbazepine. Many others are at an advanced stage of clinical trials e.g., topiramate, and tiagabine or entering clinical trials e.g. remacemide and levetiracetam (1). Inspite of all these advances, even today, the treatment of epilepsy remains far from adequate (2). The currently used antiepileptic drugs (AEDs) often fail to provide adequate seizure control, are associated with risk of toxicities and the drug–drug interactions are always a therapeutic practical problem.

The mechanisms underlying convulsions are poorly understood. However, an imbalance between excitatory and inhibitory transmission, in the brain is believed to be central to epileptogenesis. Research into pathophysiology of epileptic seizures is primarily directed towards factors responsible for initiation of seizures. But, noteworthy is the fact that seizures arrest spontaneously and abruptly and, brain remains seizure free for sometime thereafter

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i.e., the postictal refractory period (PIRP). This is observed both experimentally in animal models of seizures and clinically. It is likely that some endogenous factor(s)/ mechanism(s) are responsible for the spontaneous arrest of seizures and the PIRP (3, 4).

Why seizures arrest abruptly?

Initially, neuronal fatigue was implicated in arresting seizures but experimental studies demonstrated a concomitant increase in metabolic activity, sufficient to cope with increased demand (5). Kreisman et al (6), suggested that only in prolonged or protracted seizures (> 20 min) neuronal fatigue can play a role. Other possible mechanisms for seizure termination namely hypoxia, hypercapnia, or acidosis, also could not be validated in studies in experimental animals and have been ruled out (7). Certain brain areas, e.g. caudate, intralaminar and medial thalamic nuclei, red nucleus and some brain stem structures as potential mediators of seizure arrest and refractoriness have also been studied (8). However, the data available does not unequivocally implicate any brain area in either the spontaneous arrest of seizures or PIRP (3).

Since, the ionic environment of the brain has a profound effect upon the nervous system activity, a number of researchers have suggested that ions may be involved in seizure mechanisms. Thus magnesium ions which have a sedative action may be anticonvulsant. Increased plasma magnesium during seizures, has been observed (9). On the other hand, excess of extracellular potassium which produces depolarisation block may induce, maintain and ultimately terminate seizures (10). Similarly, chloride ions may be involved in seizure generation (11) while the role of calcium ions is being investigated (12). Although it is clear that ions are involved in pathophysiology of seizures, yet there is no evidence implicating any ion in seizure arrest or PIRP.

Is endogenous anticonvulsant substances involved?

The most attractive theory for spontaneous and abrupt arrest of seizure activity is the ictal or post-ictal release and/ or activity of endogenous anticonvulsant substances (EASs). *EASs have been defined as endogenous molecules, possessing anticonvulsant properties, released during seizure activity, exerts stabilising effects on the epileptogenic focus and surrounding neural tissues and the accumulation of which terminates seizure activity while increasing the threshold for further seizure induction (13).* A putative EAS may abort seizure activity by one or more of the following mechanisms – (a) enhancement of inhibitory mechanisms, (b) antagonism of excitatory mechanisms and (c) interference with voltage gated ion channels (14, 15). A potential candidate for a seizure activated EAS might be expected to satisfy certain biological criteria (16). These are summarised in Table I.

Putative candidates as endogenous anticonvulsant substances (EASs) -

A number of candidates have been proposed to act as EAS in different studies (Table II). These include the *catecholamine* - noradrenaline, adrenaline, dopamine; *indoleamines* - serotonin and melatonin; *histamine*; *purines* - adenosine, inosine; *opioids and other neuropeptides* –

TABLE I : Criteria for a putative endogenous anticonvulsant substance.

1.	Exogenous administration of substance should produce anticonvulsant action.
2.	The anticonvulsant effect should represent a dose–related pharmacological (receptor–mediated) action.
3.	Seizure activity should produce changes in level, receptors and/or effects of the substance.
4.	Since it has been suggested that seizure termination coincides with neuronal hyperpolarization, which is long lasting, the EAS should produce neuronal hyperpolarization.
5.	Because the EAS is not tonically active, specific antagonists would not be expeceted to influence pre–seizure or seizure activity.

cholecystokinin, somatostatin, ACTH, TRH etc.; *steroid hormones* - progesterone, thyroxine, cortisol; *prostaglandins* and *nitric oxide*.

The catecholamines, noradrenaline, adrenaline, dopamine and the indoleamines have a physiological role in the brain. In experimental animals, dopamine, noradrenaline and serotonin agonists have protective effects. Their antagonists on the other hand may be sometimes protective, sometimes weekly proconvulsant (3). The differential effects of their receptor subtypes has also been documented (29). In case of histamine, it is likely that histaminergic neuron system may be important for seizures at younger ages (35). Paradoxical findings i.e. both proconvulsant and anticonvulsant effects have also been reported for opioids and other neuropeptides present in the central nervous system (16). Thus it is apparent that none of these substances have been unequivocally shown to be an EAS.

The adenosine hypothesis of epilepsy however is finding support from both clinical and laboratory observations and is potentially a nucleus around which further experimentation can crystallize (69).

The adenosinergic system

Adenosine is a purine nucleoside, long recognised to be a local regulator of physiological function, i.e., it acts within the same organs, perhaps even on the very cells that are the sites of its production. The possibility of purinergic transmission was first considered by Holton and Holton (70). Later on, it was demonstrated that adenosine and its nucleotides have potent depressant effects on the responses of neurons at many levels of neural axis, with the hippocampus, cerebral cortex and caudate nucleus being particularly sensitive (71). Adenosine release appears to be related to metabolic activity involving increased energy consumption and may be expected to increase in situations in which ATP hydrolysis is accelerated, or in which ATP resynthesis is reduced e.g. during hypoxia and in tissues exposed to metabolic inhibitors (72).

Adenosine receptor subtypes :

The existence of specific binding sites for adenosine, the adenosine receptors was proposed in 1970 when adenosine – stimulated accumulation of cAMP in brain slices was seen to be antagonized by theophylline (73). The term purinergic receptors was originally coined for ATP receptors. Later, purinergic receptors were classified into P_1 receptors which recognize adenosine (and possibly AMP) and P_2 receptors which recognize ATP and ADP. The purinergic P_1 receptors were further subclassified on the basis of their behaviour towards adenylate cyclase. Thus A_1 inhibit

TABLE II : Putative endogenous anticonvulsant substances (EAS).

Putative EAS candidate	*Species studied*	*Seizure models / agents used*	*References*
Catecholamines			
Noradrenaline	Rat Baboon	PTZ, MES, Penicillin, Kindling, Genetic	17–22
Adrenaline	Rat Baboon	Kindling, Genetic	23, 24
Dopamine	Mice Rats Gerbil Baboon Rabbit	Genetic, Kindling, Pilocarpine-induced seizures	23, 25–29
Indoleamines			
Serotonin	Rat	PTZ, ECS, Kindling Genetic, BIC	30, 31
Melatonin	Rat Gerbil	PTZ, Kindling Genetic	32, 33
Histamine	Rat Mice	MES	34, 35
Inhibitory neurotransmitters			
GABA	Rat Mice Gerbil	KA, ECS, Genetic	36–38
Taurine	Rat	Genetic, Kindling	3
Purines			
Adenosine	Rat, Mice	Genetic, Kindling, HTL, DMCM, NMDA	39–43
Inosine	Rat	Genetic, Kindling PTZ, BIC, PTX, Kynurenine	44, 45
Prostaglandins	Rat Gerbil Mice	PTZ, MES, Fluorothyl, STR, Genetic, PTX, BIC	46–51
Opioids	Rat Baboon Mice Gerbil Rabbit	Kindling, Genetic, Fluorothyl, Penicillin, MES, PTZ	16
Neuropeptides			
ACTH	Rat	Kindling	52
TRH	Rat Cat	Kindling, Genetic ECS	53 – 56
Somatostatin	Rat Gerbil	Kindling, Genetic,	57 – 60
Cholecystokinin	Rat	Kindling	61
Steroid hormones			
Sex steroids	Mice Rat	PTX, PTZ, BIC, MES, STR, Kindling, Genetic	62 – 65
Cortisol	Gerbil Baboon	Genetic	23, 66
Nitric oxide	Mice Rat	NMDA, PTZ, Pilocarpine, Kindling, Carbachol	67, 68

PTZ - Pentylenetetrazole, MES - maximal electroshock seizures, KA - kainic acid, ECS - electroconvulsive shock, BIC - bicuculline, PTX - picrotoxin, STR - strychnine, NMDA - N-methyl-D-aspartate, DMCM - Methyl, 6, 7-dimethoxy-beta-carboline-3-carboxylate.

while A_2 stimulates adenylate cyclase. An alternative system of nomenclature uses R (for ribose) instead of A to denote adenosine receptors and subscripts 'i' for inhibitory and 'a' for stimulating subtypes respectively. In addition to these two receptors, adenosine and its analogs may be mediating their effect via another site which recognizes the purine moiety as opposed to the classical receptors which recognize the ribose moiety. This site is designated as 'P–site' (74).

Based on agonist potencies as well, the classification into A_1 and A_2 subtype holds. While R – PIA is a more potent agonist than NECA at most A_1 receptors, the opposite is true in case of A_2 receptors (74).

Recently, an adenosine A_3 receptor subtype has been cloned and its pharmacological characteristics studied (75). The A_3 adenosine receptor cloned from rat is unique among the subtypes in that agonist action is not antagonized by xanthines such as theophylline. The NC – IUPHAR Subcommittee on Purinoceptors (1996) has proposed a consensus nomenclature classifying adenosine receptors into four subtypes i.e. A_1, A_{2A}, A_{2B} and A_3 (Table III)

Molecular structure of adenosine receptor:

All adenosine receptors are the members of G protein – coupled receptor family and possess seven transmembrane helical regions (Fig. 1). The seven membrane spanning regions (designated HI to HVII), likely consist of right handed α – helices that are interconnected by three extracellular loops (EI to EIII) and three cytoplasmic loops (CI to CIII). In contrast to other G – protein coupled receptors, putative glycosylation sites have been identified on EII rather than near the amino terminus. Cytoplasmic domains contain multiple serine and threonine residues that are potential substrates for phosphorylation by protein kinase A, protein kinase C, caseine kinase 2 or β – adrenoceptor kinase, and these may also be involved in G – protein interactions. Both A_1 and A_2 receptors are known to be regulated by Na^+ and contain putative sites for interaction

TABLE III : NC-IUPHAAR consensus classification for adenosine receptors.

	Receptor subtypes			
	A_1	A_{2a}	A_{2b}	A_3
Selective Agonist	CPA, 2-CCPA GR 79236	CPCA, DPMA, PAPA-APEC, CGS 21680	- 2-chloro-IB-MECA	IB-MECA,
Selective Antagonist	DPCPX, 8-CPT	DMPX SCH 58261, DF 17837, ZM 241385	-	I-ABOPX
Effector	$G_{i/o}$	G_s	G_s	$G_{i/o}$
Gene	a1;chr 1	a2A; chr 22	a2B; chr 17	a3;chr 1
Structure				
Human	326aa	409aa	328aa	318aa
Mouse	326aa	327aa	332aa	
Rat	326aa	410aa	332aa	320aa

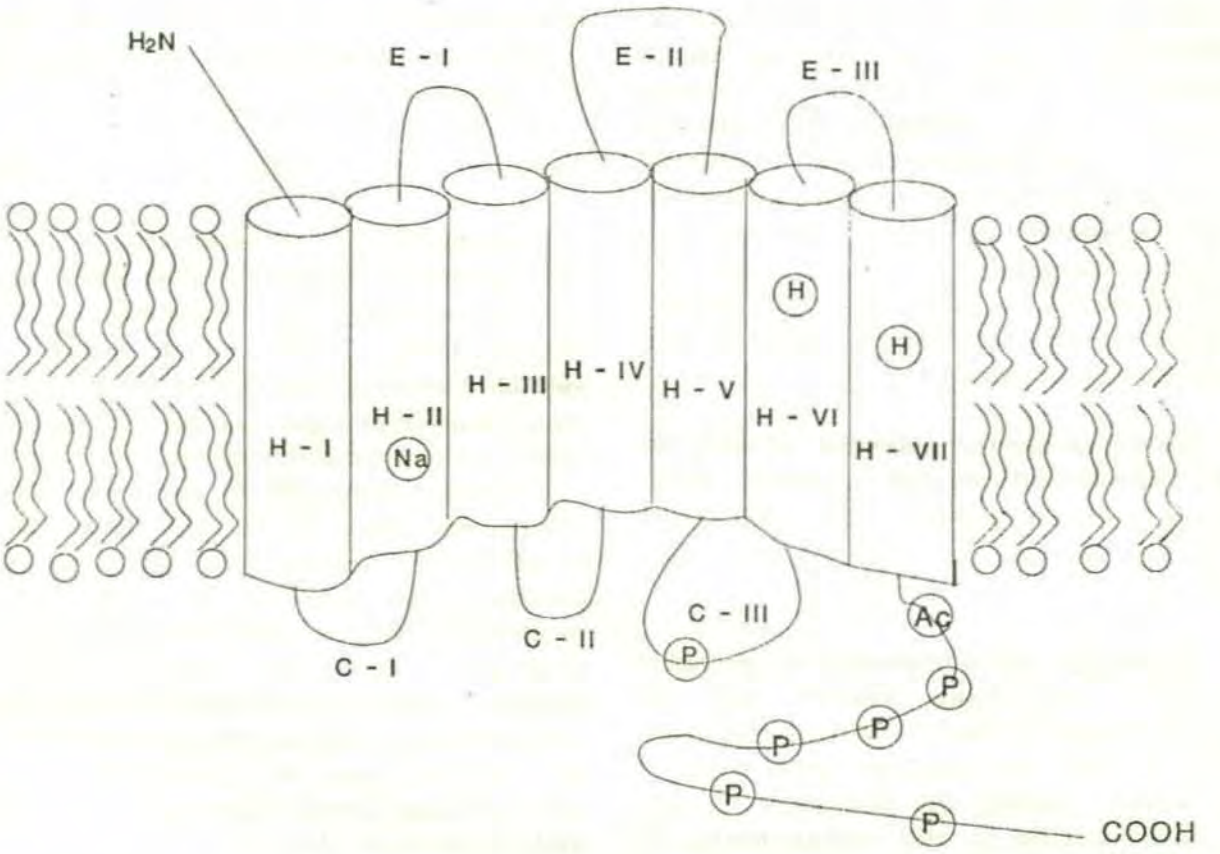

Fig. 1 : Schematic representation of domain structure of the adenosine receptor.

with Na^+ at the cytoplasmic site of HII. Two different histidine residues have been implicated in the ligand binding to both A_1 and A_2 receptors and a putative mode of interaction of histidine residues with adenosine receptor agonists and antagonists has been proposed. Likely candidates for these interactions are two conserved histidine residues in HVI and HVII (76).

Adenosinergic system in the central nervous system :

In a number of *in vivo* and *in vitro* studies, adenosine has been proposed as a neurotransmitter or neuromodulator in the central nervous system (71). Both adenosine A_1 and A_2 receptors are present in the brain. Autoradiographically, a very high density of A_1 receptors can be seen in the dendritic zones of the hippocampus, especially in the CA1 subfield, a structure particularly vulnerable to ischaemia and enriched with glutamate receptors of NMDA type. A_1 receptors are found presynaptically, and postsynaptically as well as extrasynaptically along the neuronal dendrites and on astrocytes (77).

The adenosine A_2 receptors are present on smooth muscle and endothelial cells of cerebral vessel where they mediate the

vascular effect of adenosine. The high affinity A_2 receptors are concentrated on the striatum and other dopamine rich areas, and particularly to a subgroup of medium sized spiny neurons with dopamine D_2 receptors and modify dopaminergic neurotransmission (78). A_2 receptors are present on rat astrocytes and may be responsible for the adenosine–induced cAMP accumulation observed in brain slices. Overall, brain contains amongst the highest concentration of adenosine receptor of any tissue examined.

Role of adenosinergic system in seizures

A large body of evidence from *in vitro* and *in vivo* studies implicate endogenous adenosine in spontaneous and abrupt arrest of seizures. It has been observed that adenosine, adenosine uptake inhibitors and adenosine A_1 and A_2 receptor agonists suppress epileptiform activity *in vitro* which could be reversed by adenosine antagonist theophylline (79). While, *in vivo*, in rodents, adenosine and its analogs protect against seizures induced by audiogenic stimuli (80), chemically-induced i.e. DMCM (Methyl, 6, 7-dimethoxy-beta-carboline-3-carboxylate), (40), homocysteine thiolactone (HTL), (39), N-methyl-D-aspartate (NMDA), (41) and also the electrically kindled seizures (42). Rapid elevations in brain levels of adenosine has also been documented after experimental seizures (81) as well as post-seizures in epileptic patients (82).

On the other hand, adenosine receptor antagonists theophylline and caffeine induce generalised seizures in rodents (83). The non-convulsive doses of theophylline reverse the protection of adenosine and adenosine receptor agonists (84).

In kindling model of epilepsy, A_1 and A_2 receptor agonists inhibit the development of kindling, reduce after discharge duration, the severity of behavioural seizures and increase electroencephalographically observed post-ictal depression. The adenosine receptor antagonists on the other hand have an opposite effect (42, 43).

In some later studies however, a proconvulsive action of both adenosine receptor agonists (85) and adenosine uptake inhibitor, papaverine (86) against seizures induced by theophylline or caffeine has been documented. Klitgaard et al (87), have suggested that adenosine A_1 and A_2 receptor agonists may be both anticonvulsant as well as proconvulsant in experimental animals depending on the mechanism of action of chemoconvulsant used for seizure induction.

In experiments in our laboratory, adenosine 1000 mg/kg, 5 min pretreatment showed significant protection against PTZ seizures while, a moderate decrease in seizure activity as assessed by an increase in latency of seizures was also observed with adenosine 500 mg/kg, 5 min pretreatment (88).

Adenosine has a very short half-life and is metabolised by adenosine deaminase to inosine and subsequently hypoxanthine. Some adenosine released may be taken up by specific uptake mechanisms, thus limiting its action. The degradative products have also shown pharmacological activity. Therefore studies have been done using metabolically stable analogues of adenosine like 2-chloroadenosine (2-CADO), R-phenylisopropyladenosine (R-PIA) and N^6-cyclohexyladenosine (CHA). These analogs are not substrates for either the nucleoside

transporters or the metabolizing enzyme adenosine deaminase (89).

The role of 2-CADO as anticonvulsant is rather controversial. In our experiments, 2-CADO, was only partially effective against PTZ-induced seizures in doses of 5 mg/kg and even this protection was attenuated when the dose was increased to 10 mg/kg. Though 2-CADO has greater affinity for A_1 receptors as compared to A_2 receptors, it is probable that at the higher doses it looses its selectivity and activates A_2 receptors as well (88).

Inosine is an adenosine metabolite which has also been identified as an endogenous ligand for benzodiazepine receptors, based on its capacity to bind to benzodiazepine binding site in brain and also to diazepam antibodies (90). Although this binding in the brain is low affinity as compared to the periphery still it has been proposed that this may be sufficient to induce an anticonvulsant response. In experimental models of seizures, inosine injected in the cerebral ventricles of mice prolongs the latency of seizures evoked with PTZ (91). Electroshock, bicuculline and PTZ seizures elevate inosine levels in brains of cat, mouse and rat (44, 92). It has also been demonstrated that a series of fifteen electroshocks raised inosine levels in brains of mice and subsequently, the threshold for PTZ-induced seizures was elevated. Pretreatment with phenytoin which has inosine antagonist properties or adenosine deaminase inhibitor, EHNA, reversed the rise in inosine levels as well as increased the threshold of PTZ seizures following electroshock. Although the role of inosine is not clear it is more likely to be involved in PIRP than seizure arrest (3).

Which adenosine receptor subtype(s) is/are involved in anticonvulsant effect?

Once it is established that the adenosinergic mechanism exerts an anticonvulsant action, the question that arises is how this effect is mediated? Adenosine stimulates two major receptors subtypes A_1 and A_2, which are linked to a multitude of effectors. Despite intensive investigation, a direct role for the A_1 and/or A_2 adenosine receptors in mediating the electrophysiological actions of adenosine remained elusive. This was primarily due to a lack of potent and selective adenosine A_2 receptor agonists and antagonists. However, the availability of selective and potent agonists/antagonists, for adenosine receptor subtypes in recent years has facilitated the elucidation of subtype involvement. We have studied, the differential effect of adenosine A_1 receptor agonists N^6-cyclopentyladenosine (CPA) and A_2 receptor agonist 5'-(N-cyclopropyl) carboxamidoadenosine (CPCA) in seizures induced by PTZ, in rats. The selective adenosine A_1 receptor agonist, CPA (10 mg/kg) significantly protected while, the A_2 receptor agonist, CPCA did not show protection against PTZ–induced seizures. The protection observed with CPA was even greater than that of adenosine 1000 mg/kg, 5 min, pretreatment. The protective effects of adenosine and CPA against PTZ-induced convulsions, could be reversed by both the nonspecific adenosine receptor antagonist, theophylline and DPCPX, the specific adenosine A_1 receptor agonist but not by DMPX the adenosine A_2 receptor antagonist. These findings point towards a predominantly A_1 adenosine receptor involvement in mediating the anticonvulsant action against PTZ seizures.

The protective effect of adenosine A_1 receptor stimulation against chemically induced seizures has been reported by other workers as well. However, the experimental animal models used in their studies were different i.e. NMDA seizures in mice and bicuculline– methiodide induced seizures respectively (41, 93).

The possible biochemical cascade in the anticonvulsant action of adenosine

The exact mechanism mediating the anticonvulsant effect of adenosine and adenosine A_1 receptor stimulation, is unclear. Adenosine receptors have been identified in many brain areas including hippocampus (77). These receptors in particular the A_1 receptors are linked to a multitude of effector systems (74). These include adenylate cyclase, stimulation of PI turnover, potassium and calcium channel activation and cGMP formation. An inhibitory effect on adenylate cyclase by A_1 adenosine receptor stimulation, results in decreased cAMP production. cAMP may be epileptogenic by virtue of its ability to depolarize neurons (94). The analogues of the nucleotides db-cAMP and db-cGMP are epileptogenic following i.c.v. administration in rats (95) and cats (96).

Apart from this, adenosine A_1 receptor stimulation also modulates the release of different neurotransmitters (97). This is more so in case of excitatory neurotransmitters, glutamate and acetylcholine than for the inhibitory neurotransmitters such as noradrenaline and GABA (89). Since an increase n excitatory neurotransmitters may underly epileptogenesis adenosinergic system may be eliciting the anticonvulsant effect through this pathway.

Recently, it has been shown that adenosine and 2-CADO have antioxidant properties (98). The significance of this finding is still unclear. Thus, adenosinergic system may be anticonvulsant due to any of these mechanisms or an interplay of all these biochemical changes in the central nervous system.

Do systemic effects of adenosine and its analogues contribute to their anticonvulsant response?

The two peripheral effects of importance following systemic administration of adenosine and adenosine analogs are hypotension and hypothermia. It has been contended that these peripheral effects may be somehow contributing to the protection observed with adenosinergic agents, possibly by modifying the convulsant behaviour or a direct effect. This contention has been investigated intensively in experimental animals. The extent and time course of development of both hypotension and hypothermia reveal that a relationship between hypotensive and anticonvulsant action of adenosine and adenosine receptor agonists is unlikely (88).

Is the adenosinergic system involved in the mechanism of action of the antiepileptic drugs?

Several lines of evidences suggest that adenosine may be involved in the mechanism of action of chemically and mechanistically diverse antiepileptic drugs namely, benzodiazepines, barbiturates and carbamazepine. Benzodiazepines have been shown to inhibit adenosine uptake (99). A

physiological role for adenosine has been suggested in the benzodiazepine receptor chloride channel complex (40). Thus benzodiazepines potentiate the depressant actions of adenosine on the firing of cerebral cortical neurons (100). This action of diazepam is shared by flurazepam and, theophylline reverses this effect (101).

Among the barbiturates, pentobarbitone displaces the binding of phenylisopropyladenosine (PIA), from brain slices and inhibited the suppression of adenylate cyclase (102). In a more recent study, it had no effect on the depressant effect of adenosine in hippocampal slices (103). There have been however, attempts to identify the adenosine receptors with binding site for barbiturates (104).

The iminostilbine, carbamazepine diminishes adenosine's effects on smooth muscle contraction, neuronal firing, adenylate cyclase activation and synaptic activity (103, 105). Carbamazepine treatment also upregulates adenosine receptors in rats (106).

In our experiments, the nonspecific adenosine receptor antagonist, theophylline *per se* in doses that do not induce convulsions reversed the protection afforded by all the drugs i.e. diazepam, sodium valproate, phenobarbitone and carbamazepine, against PTZ seizures, though to a variable extent. The highly specific adenosine A_1 receptor antagonist DPCPX however, could not reverse the seizure protective effect of either of the antiepileptic drugs (107). The dose of the adenosine A_1 receptor antagonist DPCPX used in these studies has been demonstrated to be sufficient for effectively blocking adenosine A_1 receptors *in vivo* (108). The same dose of DPCPX i.e. 1 mg/kg, has also been used by other workers for adenosine A_1 receptor antagonism in different experimental paradigms (41, 109). Czuczwar et al (110), have also demonstrated that protection of diazepam, phenobarbitone, and valproate in maximal electroshock seizures in mice, was not reversed by CGS 15943 A, a nonxanthine antagonist at adenosine A_1 receptor. Thus, the involvement of adenosine A_1 receptors in the anticonvulsant action of antiepileptic drugs appears to be unlikely.

The augmented protection on combining subanticonvulsant doses of adenosinergic agonists and the common antiepileptic drugs: Reasons and implications.

Interestingly, it has been observed that when subanticonvulsant doses of diazepam and sodium valproate, are combined with either adenosine or CPA, in doses that were subanticonvulsant against PTZ seizures, there was a significant reduction in the incidence of generalized clonic seizures as compared to either drug alone (107). Such an augmentation has also been observed by other workers (111). The mechanism underlying this augmented protection however remains conjectural.

Can adenosine be regarded as an endogenous anticonvulsant substance?

Adenosine appears to be meeting the different biological criteria put forth by Tortella (16) for an endogenous anticonvulsant substance. It is found endogenously, exogenous administration has an anticonvulsant action, the action being dose related. This effect is mediated by a

particular receptor subtype i.e. A_1 receptors. The specific adenosine A_1 receptor antagonist DPCPX neither *per se* causes convulsions nor does it aggravate seizure activity in rats. This can be taken to mean that adenosine is perhaps not tonically active but is rather brought into play by the seizure itself.

Another criteria for an EAS is that seizure activity should produce changes in level, receptors and/or effects of the substance. Though the estimation of the levels of adenosine and its metabolites has not been done yet by us, the attempts are being made to conduct such studies which will provide confirmatory evidence. The reports are available that suggest an alteration in the level of adenosine and its metabolites after convulsant challenge/ seizures. It has been documented that maximal electroshock and bicuculline induced seizures bring about a rapid increase in the brain levels of adenosine and its metabolites in experimental animals (81).

Therapeutic implications

The finding that adenosinergic system is intimately involved in seizure activity and that the adenosine A_1 receptor subtypes are involved predominantly has a wide range of clinical implications. It will not only help in understanding the pathophysiology of epileptic seizures which todate is poorly understood. But it is likely that a defect in adenosinergic system i.e., synthesizing or metabolizing enzymes, receptors and effectors may be involved. This of course can not be generalized to all forms of epilepsy, i.e. it may not be a common effector but it certainly may be crucial for at least some forms of epilepsies. For e.g. in status epilepticus (i.e. prolonged and recurrent seizure activity), loss of endogenous mechanisms that generally arrest seizures might be one of the critical event mediating the transition from single brief seizures to the protracted and recurrent episodes of status epilepticus.

Clinical implications :

Adenosine *per se*, due to its rapid inactivation in the body and its potent cardiovascular, respiratory and sedative effects, may not offer a good potential for therapeutic exploitation. However, adenosine analogues, specifically A_1 receptor agonists, deaminase inhibitors or uptake blockers might prove to be useful anticonvulsants. Since, the peripheral effects do not contribute to the observed protection, the drug development may be targetted to design specific agents in which these two effects can be separated. The usefulness of adenosinergic modulating agents for treatment of refractory cases and status epilepticus is an important area, that needs to be explored. Logically, it may be possible to use short acting adenosine analogues to terminate an episode of status epilepticus. Since the treatment of status epilepticus would require a hospital setting, with facilities to monitor patients and maintain vital functions. Theoretically, adenosine infusions may also prove to be useful since the dose can be titrated based on the patient response. Adenosine has mild and transient side effects and has already been marketed in the U.S. for supraventricular tachycardias. However, there is need to generate data on this aspect i.e. utility for aborting an attack of status

epilepticus, both *in vivo* and subsequently in the clinics.

Furthermore, though the involvement of adenosinergic mechanisms in the action of commonly used antiepileptic drugs seems unlikely, the results indicate that combination with adenosinergic agents may potentiate the effect of these drugs. Thus, adenosinergic agents may have value as adjuncts to enhance the efficacy and perhaps reduce the dose and related toxicities of antiepileptic drugs.

Adenosine and its metabolites as diagnostic markers?

From the above discussion it follows that adenosine levels could also be considered as diagnostic markers for certain types of epilepsies. If the defect in adenosinergic system is of genetic origin, such a diagnostic test will be of special significance. However till more studies in this direction are carried out, it remains conjectural.

CONCLUSION

It is obvious from the above discussion that adenosinergic agents have an anticonvulsant action and this action is primarily mediated via adenosine A_1 receptors. Since adenosinergic system satisfies almost all the criteria put forth for an endogenous anticonvulsant substance, it may well be responsible for spontaneous and abrupt arrest of seizures. The important clinical implications of these findings can not be ignored and require further validation.

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