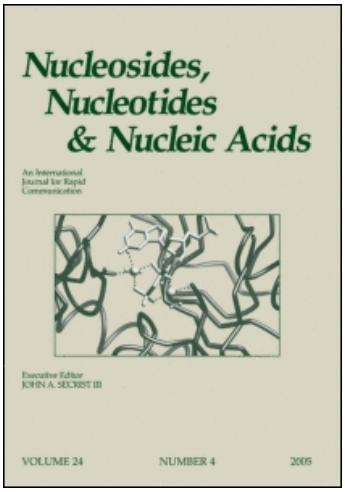

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THE INFLUENCE OF ADENOSINE RECEPTOR ANTAGONISTS AMINOPHYLLINE (AMP) AND CAFFEINE (CAF) ON SEIZURE PROTECTIVE ABILITY OF ANTIEPILEPTIC DRUGS (AEDs) IN RATS

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Abstract : The acute effects of AMP and CAF on seizure protectivity of AEDs were examined against electro and chemo shock convulsions in rats. The results support the claim that adenosine receptors may be involved in action of some AEDs.

Adenosine and its nucleotides modulate CNS synaptic transmission. The role of adenosine as the brain's natural anticonvulsant is well established and its levels are reported to increase markedly following a seizure, thus terminating it. AMP and CAF antagonise the effects of adenosine at A_1 and A_2 receptor sites. In view of the local incidence of clinical epilepsy coexisting with chronic bronchial asthma, this study addresses itself to the lowering of seizure protective efficacy of AEDs by AMP or CAF.

Experiments were carried out in Wistar rats (180-200g). Subconvulsant doses of AMP (100 mg/kg, ip) or CAF (200 mg/kg, ip) were administered to rats pretreated 15 mins prior to AEDs, Viz. Phenytoin (DPH); Carbamazepine (CBZ); Phenobarbitone (PB); Diazepam (DZP); Sodium valproate (SV) and Ethosuximide (ESM) at their predetermined ED_{100} doses (mg/kg ip). Maximal electroshock (MES) or pentylenetetrazol (PTZ), 70 mg/kg sc, was given following pretreatment with AMP or CAF at the peak efficacy time of AEDs. All the animals treated with AEDs, except ESM, were subjected to MES and PTZ test, was carried out in rats pretreated with AEDs except DPH. Alteration in 100% seizure protective ability was determined.

The results show that in the MES test, the 100% seizure protection afforded by all the AEDs (with the exception of SV) declined to 20%, following AMP. On the other hand, following CAF, the 100% protection by DPH, DZP & CBZ was completely reversed and PB was lowered to 20%. The absolute seizure protectivity of SV remained unimpaired either by AMP or CAF, showing a qualitative departure in its activity profile.

In the PTZ test, the % protective activity of PB and DZP was reduced to 0 and 20% respectively, following AMP, whereas protectivity of both PB & DZP were completely reversed following CAF. However, seizure protective action of SV and ESM against PTZ remained uninfluenced, following interaction with AMP or CAF.

The results of the above experiments clearly indicate that -

1. Adenosine receptor antagonists, AMP & CAF had qualitatively different effects on absolute seizure protection afforded by commonly used AEDs in MES & PTZ tests ;
2. This differential action suggests that anticonvulsant effects of SV and ESM may not involve adenosine receptor sites.
3. Interaction of AEDs with AMP or CAF differentiates the drugs used for tonic clonic seizures, viz. DPH, PB, CBZ, SV and DZP (in status epilepticus) and for absence seizures, viz. ESM & SV.
4. This distinctive feature of SV could be of particular interest as it may be recommended as the drug of choice in epilepsy coexisting with bronchial asthma.

Clinical studies are contemplated in order to substantiate the above findings.