2-Chloro-N⁶-cyclopentyladenosine enhances the anticonvulsant action of carbamazepine in the mouse maximal electroshock-induced seizure model

Jarogniew J. Łuszczki¹,⁎, Maria Kozicka², Mariusz J. Świąder², Stanisław J. Czuczwar¹,³

¹ Department of Pathophysiology, Medical University of Lublin, Jaczewskiego 8, PL 20-090 Lublin, Poland
² Department of Pharmacology and Toxicology, Medical University of Lublin, Jaczewskiego 8, PL 20-090 Lublin, Poland
³ Department of Physiopathology, Institute of Agricultural Medicine, Jaczewskiego 2, PL 20-950, Lublin, Poland

Correspondence: Jarogniew J. Łuszczki, e-mail: jarogniew.luszczki@am.lublin.pl
* Recipient of the Fellowship for Young Researchers from the Foundation for Polish Science.

Abstract:
This study examines the anticonvulsant profile of interactions between 2-chloro-N⁶-cyclopentyladenosine (CCPA, a selective adenosine A₁ receptor agonist) and four conventional antiepileptic drugs (AEDs: carbamazepine – CBZ, phenobarbital, phenytoin and valproate) in the mouse maximal electroshock seizure (MES) model. Acute adverse effects produced by AEDs in combination with CCPA were determined in the chimney test (motor performance) and passive avoidance task (long-term memory).

Results indicate that CCPA administered alone at 0.25 and 0.5 mg/kg significantly elevated the electroconvulsive threshold in mice. Additionally, the agent at a sub-threshold dose of 0.125 mg/kg potentiated the anticonvulsant activity of CBZ by reducing its ED₅₀ in the MES test from 11.2 to 7.7 mg/kg (p < 0.01). In contrast, 8-cyclopentyl-1,3-dimethylxanthine (DPCPX, a selective adenosine A₁ receptor antagonist at 5 mg/kg) abolished the enhanced anticonvulsant effects offered by the combination of CBZ with CCPA (0.125 mg/kg). Moreover, CCPA (0.125 mg/kg) co-administered with other tested AEDs had no significant impact on their antiseizure properties in the MES test in mice. Neither CCPA (0.125 mg/kg) administered singly, nor in combinations with conventional AEDs (at their ED₅₀) affected motor performance in the chimney test and long-term memory in the passive avoidance task.

No pharmacokinetic alterations in brain CBZ concentrations were observed after administration of CCPA at 0.125 mg/kg.

It may be concluded that CCPA, acting selectively on adenosine A₁ receptors, enhances pharmacodynamically the antiseizure effect of CBZ in the MES test.

Key words:
2-Chloro-N⁶-cyclopentyladenosine, carbamazepine, maximal electroshock, adenosine A₁ receptors, antiepileptic drugs