

EFFECT OF ADENOSINE RECEPTOR AGONISTS ON NEURODEGENERATIVE AND CONVULSIVE ACTIVITY OF MITOCHONDRIAL TOXIN, 3-NITROPROPIONIC ACID

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3-Nitropropionic acid (3-NPA) is a mitochondrial toxin inhibiting the activity of succinate dehydrogenase. Its experimental application in rodents causes lesions of the striatum resembling the course of Huntington's disease in humans. Recently, we have shown that 3-NPA is also a potent convulsive and proconvulsive agent. This study investigated the effects of adenosine receptor agonists on neurodegeneration and convulsions induced by 3-NPA. Adenosinergic agonists prevented seizures but not striatal neuronal loss evoked by 3-NPA, what suggests that different mechanisms might contribute to these pathologies associated with application of mitochondrial toxin.

Key words: *3-nitropropionic acid, mitochondrial toxin, seizures, neurodegeneration, adenosine*

Increasing number of data implicate that altered cellular energy metabolism might contribute to the pathogenesis of neurodegenerative and convulsive diseases [4]. Mitochondrial toxins are substances compromising the oxidative phosphorylation and ATP synthesis *via* interference with the mitochondrial respiratory chain. It was found that 3-nitropropionic acid (3-NPA), irreversible inhibitor of succinate dehydrogenase (mitochondrial complex II), commonly occurring in nature, causes numerous alteration of CNS function upon accidental ingestion in humans [5]. Further studies revealed that experimental application of 3-NPA in rodents led to selective neuronal degeneration within basal ganglia and behavioral symptoms, resembling the course of Huntington's disease [1, 5]. Recently, we have shown that 3-NPA is a potent convulsant in rodents, able to display proconvulsive properties as well [3, 6, 7]. 3-NPA-evoked seizures may be inhibited by only some of the anticonvulsive drugs such as diazepam, phenobarbital and valproate [6]. Glutamate receptor antagonists of the non-NMDA type also proven effective against seizures caused by 3-NPA [7].

Adenosine is an endogenous inhibitory modulator of synaptic transmission and neuronal activity, interacting with specific membrane receptors. Adenosine displays an anticonvulsant action in different experimental models and may contribute to the depressed responsiveness of neurons after the period of discharge [2]. The present study was designed to evaluate the effect of adenosine receptor agonists on 3-NPA-induced convulsions and neuronal loss.

The studies were carried out on male Albino Swiss mice weighing 20–25 g and male Wistar rats weighing 250–300 g. The substances used in the study included: 3-nitropropionic acid (3-NPA; Sigma, USA), A₁ adenosine receptor agonist – R-N⁶-phenylisopropyladenosine (R-PIA; Sigma, USA), A₁/A₂ adenosine receptor agonist – 2-chloroadenosine (2-CADO; Sigma, USA). Convulsions were evoked by intraperitoneal (*ip*) administration of 3-NPA at the dose of 210 mg/kg, equal to its CD₉₇ (dose of drug causing seizures in 97% of the studied animals). R-PIA and 2-CADO were given *ip* 15 min prior to the injection of the convulsant. Intra-striatal injections of 3-NPA were performed in stereotaxic apparatus in anesthetized rats, 3-NPA (0.3 mol) was microinjected into the right striatum. 3-NPA-lesioned animals were decapitated 72 h

after the surgery. Evaluation of striatal damage was based on the measurements of glutamic acid decarboxylase (GAD) activity.

A₁ adenosine receptor agonist, R-PIA, prevented the development of seizures induced by *ip* application of 3-NPA with ED₅₀ value (the dose of drug inhibiting seizures in 50% of the studied animals) of 1.5 (0.7–3.3) mg/kg. Similarly, A₁/A₂ adenosine receptor agonist, 2-CADO, displayed anticonvulsant activity with ED₅₀ of 3.5 (1.7–7.1) mg/kg. Moreover, R-PIA and 2-CADO reduced the mortality caused by the convulsant with ED₅₀ of 1.75 (0.8–3.8) and 2.9 (1.2–6.6) mg/kg, respectively. In contrast, the peripheral application of both studied here adenosine agonists did not affect the degree of neuronal loss evoked by 3-NPA, as revealed by GAD measurements.

The obtained results suggest that the activation of adenosine receptors might play a role in the pathomechanism of seizures occurring after 3-NPA administration, but not in the neurodegeneration following its intra-striatal application. Possibly, different mechanisms might be involved in the development of neuronal loss and generation of seizures evoked by 3-NPA.

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