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Paradoxical effects of adenosine receptor ligands on hydroxyl radical generation by L-DOPA in the rat striatum

Krystyna Gołembiowska, Anna Dziubina, Magdalena Kowalska, Katarzyna Kamińska

Institute of Pharmacology, Polish Academy of Sciences, Smętna 12, PL 31-343 Kraków, Poland

Correspondence: Krystyna Gołembiowska, e-mail: nfgolemb@cyf-kr.edu.pl; www.if-pan.krakow.pl

Abstract:
Parkinson's disease (PD) is a progressive neurodegenerative disorder associated with selective loss of dopaminergic neurons in substantia nigra pars compacta. Among the proposed mechanisms of dopaminergic degeneration, oxidative stress is believed to play an important role. On the other hand, L-DOPA used as the main medication in PD and overproduction of dopamine (DA) in striatal neurons could elicit toxic effects due to formation of free radicals (FRs). Adenosine, an endogenous neuromodulator was shown in various experimental models to have neuroprotective properties. In our study, we investigated the role of adenosine A_1 and A_{2A} receptor ligands in hydroxyl radical generation by L-DOPA in the rat striatum. The hydroxyl radical was assayed by HPLC-ED as a product of its reaction with p-hydroxybenzoic acid (PBA). Intrastriatal infusion of L-DOPA (50 μM) markedly increased dialysate level of DA and 3,4-dihydroxybenzoic acid (3,4-DHBA). An adenosine A_1 receptor agonist N^6-cyclopentyladenosine (CPA, 25–50 μM), non-selective A_1/A_{2A} receptor agonist 2-chloroadenosine (2-CADO, 50–100 μM), and selective A_{2A} receptor agonist CGS 21680 (25–50 μM) decreased the level of 3,4-DHBA. A non-selective A_1/A_{2A} adenosine receptor antagonist caffeine (100 μM) produced similar effect on 3,4-DHBA level. At the same time, CPA and 2-CADO, but not CGS 21680 or caffeine, decreased L-DOPA-induced DA release. The adenosine receptor ligands alone only weakly changed extracellular DA level and did not influence hydroxyl radical production. However, they showed scavenging activity in Fenton reaction *in vitro*. The primary caffeine metabolite in rodents, 1,3,7-trimethyl uric acid (1,3,7-mUA) decreased both, DA synthesis and 3,4-DHBA level. Thus, paradoxically, both agonists of A_1 receptor and agonist of A_{2A} receptor as well as antagonist of A_1 and A_{2A} receptors (caffeine), all decreased generation of FRs. Our study suggests that a decrease in hydroxyl radical generation caused by adenosine receptor ligands results from attenuation of L-DOPA-induced DA release or from their scavenging activity.

Key words:
hydroxyl radical, L-DOPA, adenosine, *in vivo* microdialysis