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Therapeutic potential of adenosine A_{2A} receptor antagonists in Parkinson's disease

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Abstract

In the pursuit of improved treatments for Parkinson's disease (PD), the adenosine A_{2A} receptor has emerged as an attractive nondopaminergic target. Based on the compelling behavioral pharmacology and selective basal ganglia expression of this G-protein-coupled receptor, its antagonists are now crossing the threshold of clinical development as adjunctive symptomatic treatment for relatively advanced PD. The antiparkinsonian potential of A_{2A} antagonism has been boosted further by recent preclinical evidence that A_{2A} antagonists might favorably alter the course as well as the symptoms of the disease. Convergent epidemiological and laboratory data have suggested that A_{2A} blockade may confer neuroprotection against the underlying dopaminergic neuron degeneration. In addition, rodent and nonhuman primate studies have raised the possibility that A_{2A} receptor activation contributes to the pathophysiology of dyskinesias—problematic motor complications of standard PD therapy—and that A_{2A} antagonism might help prevent them. Realistically, despite being targeted to basal ganglia pathophysiology, A_{2A} antagonists may be expected to have other beneficial and adverse effects elsewhere in the central nervous system (e.g., on mood and sleep) and in the periphery (e.g., on immune and inflammatory processes). The thoughtful design of new clinical trials of A_{2A} antagonists should take into consideration these counterbalancing hopes and concerns and may do well to shift toward a broader set of disease-modifying as well as symptomatic indications in early PD.

Keywords: Adenosine A_{2A} receptor; Caffeine; Dyskinesia; Neuroprotection; Parkinson's disease; Striatum

Abbreviations: 6-OHDA, 6-hydroxydopamine; ACh, acetylcholine; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; APEC, 2-[(2-aminoethylamino)carbonylethyl-phenylethylamino]-5′-ethylcarboxa midoadenosine; cAMP, adenosine 3′,5′-cyclic monophosphate; CGS 21680, 2-*p*-(2-carbonyl-ethyl)phenylethylamino-5′-*N*-ethylcarboxamidoadenosine; CHPG, (*RS*)-2-chloro-5-hydroxy-phenylglycine; CNS, central nervous system; COMT, catechol-*O*-methyltransferase; CREB, cAMP regulatory element-binding protein; CSC, 8-(3-chlorostyryl)caffeine; DARPP-32, dopamine and adenosine 3′ 5′ cyclic-monophosphate-regulated phosphoprotein 32 kDa; DAT, dopamine transporter; DMPX, 3,7-dimethyl-1-propargylxanthine; DOPAC, dihydroxyphenylacetic acid; EPSP, excitatory postsynaptic potential; GABA, γ-amino-butyric acid; GP, globus pallidus; GPCR, G-protein-coupled receptor; GPe, globus pallidus pars externa; GPi, globus pallidus interna; HD, Huntington's disease; IEG, immediate early gene; IPSC, inhibitory postsynaptic current; KF 17837, (*E*)-8-(3,4-dimethoxystyryl)-1,3-dipropyl-7-methylxanthine; KO, knockout; KW-6002, (*E*)-1,3-diethyl-8-(3,4-dimethoxystyryl)-7-methyl-3,7-dihydro-1*H*-purine-2,6-dione; L-dopa, L-dihydroxyphenylalanine; LID, L-dopa-induced dyskinesia; LTP, long-term potentiation; MAO, monoamine oxidase; mGlu5, metabotropic glutamate subtype 5 receptor; MPP^+, 1-methyl-4-phenylpyridinium; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MSX-2, 3-(3-hydroxypropyl)-8-(*m*-methoxystyryl)-7-methyl-1-propargylxanthine; MSX-3, MSX-2 phosphate disodium salt; NAc, nucleus accumbens; NGFI, nerve growth factor-induced clone; NMDA, *N*-methyl-D-aspartate; PD, Parkinson's disease; PKA, protein kinase A; PKC, protein kinase C; PPI, prepulse inhibition; REM, rapid eye movement; SCH 58261, 7-(2-phenylethyl)-5-amino-2-(2-furyl)-pyrazolo-[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidine; SKF 38393, 1-phenyl-7,8-dihydroxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine HCL; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus; TH, tyrosine hydroxylase; UPDRS, unified PD rating scale; VTA, ventral tegmental area; WT, wild type; ZM 241385, 4-(2-[7-amino-2-{2-furyl}{1,2,4}triazolo{2,3-*a*}{1,3,5}triazin-5-yl amino]ethyl)phenol.

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