Adenosine A2A Receptor Antagonists: Potential Therapeutic and Neuroprotective Effects in Parkinson's Disease

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The most effective treatment of Parkinson's disease (PD) is, at present, the dopamine precursor L-3,4-dihydroxyphenylalanine (L-DOPA), however a number of disadvantages such as a loss of drug efficacy and severe side-effects (psychoses, dyskinesias and on-off phenomena) limit long-term, effective utilisation of this drug. Recent experimental studies in which selective antagonists of adenosine A2A receptors were used, have shown an improvement in motor disabilities in animal models of PD. The A2A antagonist [7-(2-phenylethyl)-5-amino-2-(2-furyl)-pyrazolo-(4,3-e)-1,2,4-triazolo(1,5-c)pyrimidine] (SCH 58261) potentiated the contralateral turning behavior induced by a threshold dose of l-DOPA or direct dopamine receptor agonists in unilaterally 6-hydroxyparkamol (6-OHDA) lesioned rats, an effect accompanied by an increase in Fos-like-immunoreactivity in neurons of the lesioned striatum. Likewise, other A2A receptor antagonists such as [3,7-dimethyl-1-propargylxanthine] (DMPX), [\(\varepsilon\)-8-(3,4-dimethoxystyril)-1,3-dipropyl-7-methylxanthine] (KF 17837) and [\(\varepsilon\)-1,3-dietyl-8(3,4-dimethoxystyril)-7-methyl-3,7-dihydro-1H-purine-2,6-dione] (KW 6002) antagonized catalepsy induced by haloperidol or reserpine in the rat, whereas in non-human primate models of PD, KW 6002 reduced the rigidity and improved the disability score of MPTP-treated marmosets and cynomolgus monkeys. Moreover, in contrast to l-DOPA, selective A2A receptor antagonists administered chronically did not produce dyskinesias and did not evoke tolerance in 6-OHDA and MPTP models of PD. An additional therapeutic potential of adenosine A2A antagonists emerged from studies showing neuroprotective properties of these compounds in animal models of cerebral ischemia and excitotoxicity, as well as in the (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) (MPTP) model of PD. Adenosine A2A receptor antagonists by reversing motor impairments in animal models of PD and by contrasting cell degeneration are some of the most promising compounds for the treatment of PD.

Keywords: Parkinson's disease; adenosine A2A receptor antagonists; neuroprotection; dopamine D\textsubscript{1} and D\textsubscript{2} receptors; turning behavior; dyskinesia; striatum

Abbreviations: AC, adenosine cyclase; AD, adenosine; cAMP, cyclic adenosine monophosphate; CGS 15943, 5-amino-9-chloro-2-(2-furyl)-1,2,4-triazolo[1,5-c]quinazoline; CGS 21680, 2-[4-(2-carbonyl-ethyl)-phenethylamino]-5'-N-ethylcarboxamidoadenosine; CP, caudate-putamen; CP 66713, 4-amino-1-phenyl-[1,2,4]-triazolo[4,3-a]quinazoline; CSC, 8-(3-chlorostyril)caffeine; DA, dopamine; DMPX, 3,7-dimethyl-1-propargylxanthine; DYN, dynorphin; ENK, enkephalin; GABA, \(\gamma\)-aminobutyric acid; Glu, glutamic acid; GP, globus pallidus; 2-HE-NECA, 2-hexyl-5'-N-ethylcarboxamidoadenosine; KFI7837, (E)-1,3-dipropyl-8(3,4-dimethoxystyril)-7-methyl-3,7-dihydro-1H-purine-2,6-dione; KW

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6002. (E)-1,3-diethyl-8-(3,4-dimethoxystyryl)-7-methyl-3,7-dihydro-1H-purine-2,6-dione; 1-DOPA, L-3,4-dihydroxyphenylalanine; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; 6-OHDA, 6-hydroxypoline; PD, Parkinson's disease; SCH 58261, 5-amino-7-(2-phenylethyl-2(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine; SNr, substantia nigra pars reticulata; S;P, substance P; STN, subthalamic nucleus; TH, thalamus; ZM 241385, 4-[2-(7-amino-2-(2-furyl)-1,2,4-triazolo [2,3-a] [1,3,5]triazin-5-ylamino)ethylphenol

ADENOSINE AND ITS RECEPTORS

Adenosine, which is formed within the cells from the hydrolysis of AMP by the action of ecto-5' nucleotidase, modulates a variety of physiological processes in all tissues of mammals. Another pathway contributing to intracellular adenosine formation is from S-adenosylhomocysteine. In the extracellular compartment, the levels of adenosine also depend upon the rate of hydrolysis of ATP which is released from either neurons or glial cells. Extracellularly, adenosine concentrations are kept in equilibrium by a specific reuptake mechanism occurring through the action of a specialised bi-directional transporter. It is estimated that the levels of adenosine in the CNS range between 30 and 300 nM. Adenosine is then catabolised by the action of enzymes such as adenosine kinases and adenosine deaminase.

The action of adenosine is mediated through specific receptors located on cell membranes which belong to the family of G protein-coupled receptors. Currently, four adenosine receptors have been cloned and characterised: A₁, A₂A, A₂B and A₃ (Fredholm et al., 1998). The main intracellular signaling pathways of these receptors are through the formation of cAMP, with A₁ and A₃ causing inhibition of adenylate cyclase, whereas A₂A and A₂B activate it. Other transduction mechanisms are also involved for each of the adenosine receptors, e.g. K⁺ and Ca²⁺ channels. The molecular characteristics of adenosine receptors and intracellular signaling are described in detail elsewhere (Fredholm et al., 1998; Olah and Stiles, 2000). Among adenosine receptors, A₂A receptors seem to play the most important role in the modulation of motor behavior. Their molecular, pharmacological and biochemical profiles and their distribution in the CNS are summarized in Table I.

DISTRIBUTION OF ADENOSINE A₂A RECEPTORS IN THE CNS

Adenosine A₂A receptors are predominantly located in basal ganglia structures (striatum, globus pallidus, substantia nigra), nucleus accumbens and tuberculum olfactorium (Jarvis and Williams, 1989; Rosin et al., 1998). There are A₂A receptors in other brain areas, e.g. hippocampus, cerebral cortex and thalamic nuclei (Table I), with some differences found between the human brain and that of other animal species (Svenningsson et al., 1997a). It remains, however, that using different methodological approaches all studies are consistent in describing high levels of A₂A receptors in the striatum. With regard to specific neuronal populations in the striatum, A₂A receptors are present in striatopallidal enkephalin-expressing neurons (Schiffmann et al., 1991; Fink et al., 1992). The same cells also express dopamine D₂ receptors, therefore both A₂A and D₂ receptors are segregated on the same neuronal pathway. In contrast, there are no A₂A receptors in neurons expressing D₁ receptors, substance P and dynorphin, which project from striatum to the substantia nigra (Schiffmann et al., 1991; Fink et al., 1992). It is worth noting that A₂A receptors are also present on glial cells.

ADENOSINE–DOPAMINE INTERACTION AS A BASIS FOR SEARCHING ANTIPARKINSONIAN DRUGS

Increasing number of studies suggest that adenosine A₂A receptors interact, either directly or indirectly, with different neurotransmitters