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Research report

A novel adenosine A_1 and A_{2A} receptor antagonist ASP5854 ameliorates motor impairment in MPTP-treated marmosets: Comparison with existing anti-Parkinson's disease drugs

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ABSTRACT

Recent evidence indicates that adenosine A_{2A} receptor antagonists hold therapeutic potential for the treatment of Parkinson's disease (PD). A study on the novel adenosine A_1 and A_{2A} receptor dual antagonist 5-[5-amino-3-(4-fluorophenyl)pyrazin-2-yl]-1-isopropylpyridine-2(1*H*)-one (ASP5854) showed it to be effective in various rodents models of PD and cognition. In the present study, we further investigated the potential of ASP5854 as an anti-PD drug using 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated common marmosets, which is a highly predictive model of clinical efficacy in PD, and compared its effect with those of existing anti-PD drugs. ASP5854 significantly and dose-dependently improved the total motor disability score for 7 h at doses higher than 1 mg/kg, and significantly increased total locomotor activity at doses higher than 0.1 mg/kg without adverse effects. L-3,4-Dihydroxyphenylalanine + benserazide and bromocriptine also significantly improved the motor disability score and the hypolocomotion caused by MPTP treatment in a dose-dependent fashion. This amelioration was significant at 32 + 8 and 10–32 mg/kg, respectively, although bromocriptine induced severe emesis. Trihexiphenidyl also significantly improved the total motor disability score at doses of 10–32 mg/kg; however, while a significant increase in the total locomotor activity was observed at 10 mg/kg, the drug induced ataxia-like behavior at 32 mg/kg. On the other hand, neither selegiline nor amantadine improved the total motor disability and hypolocomotion. These data substantiate the evidence that the novel adenosine antagonist ASP5854 exerts comparable anti-PD activity with existing anti-PD drugs, which indicates that ASP5854 might have potential to ameliorate motor deficits in PD.

1. Introduction

The current standard treatment for Parkinson's disease (PD) is based on dopamine replacement therapy using L-3,4-dihydroxyphenylalanine (L-DOPA), dopamine agonists and/or dopamine-metabolizing enzyme inhibitors. While it produces a reliable outcome in terms of efficacy, the long-term use produces fluctuation of the efficacy (wearing-off and/or on-off) or involuntary movement (dyskinesia, dystonia and so on). These dopaminergic side-effects, motor complications, often limit their uses; therefore, a new therapy for disease management by non-dopaminergic drugs is needed, especially for the middle to late stages of the illness [19]. On the other hand, in the treatment of PD, there are non-dopaminergic anti-PD drugs like anticholinergics and amantadine, however these drugs also have some problems. While anticholinergic drugs have been used for many years, they also have side-effects, such as cognitive impairment and frontal dysfunction [2,11,39], which recently have been suggested to be irreversible [35]. The efficacy of amantadine for treatment of PD is more modest [6]; therefore, its use is thought to be suitable for early phase PD. As a consequence, current overall PD treatment is not satisfactory, and novel approaches, preferably involving novel non-dopaminergic mechanisms, are required to meet the unmet medical needs of PD patients.

Selective adenosine A_{2A} receptor antagonists have attracted attention for their potential use in the treatment of PD. Adenosine A_{2A} receptors are specifically localized in the striatum [20], where they are coexpressed with dopamine D_2 receptors in the GABAergic striatopallidal neuron [14,27]. Stimulation of adenosine A_{2A} recep-

Abbreviations: ASP5854, 5-[5-amino-3-(4-fluorophenyl)pyrazin-2-yl]-1-isopropylpyridine-2(1*H*)-one; L-DOPA, L-3,4-diydroxyphenylalanine; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.

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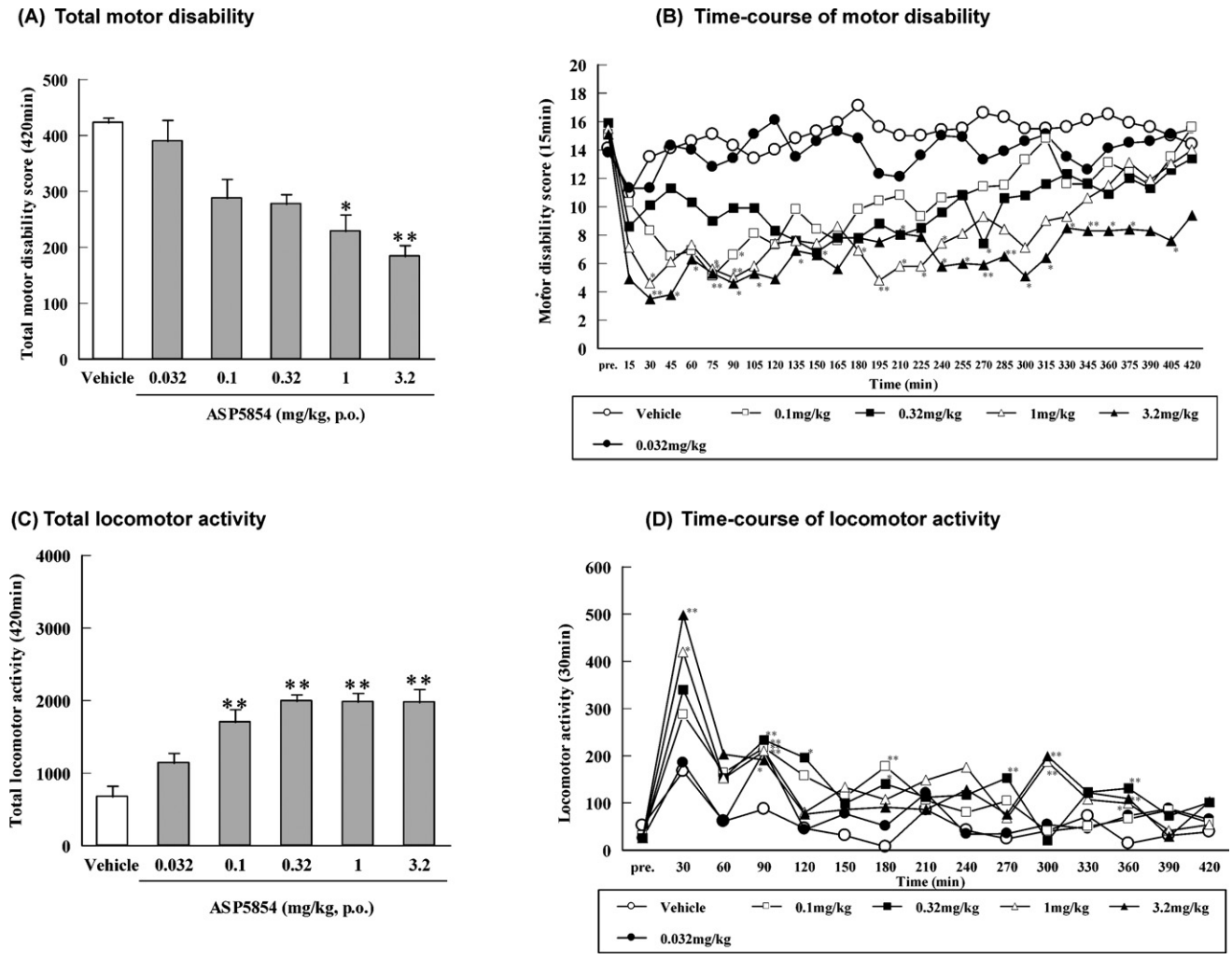

Fig. 1. ASP5854 ameliorates motor disability in MPTP-treated marmosets. (A) Dose response effect of ASP5854 on the total motor disability score. (B) Time course of the effect of ASP5854 on motor disability. (C) Dose response effect of ASP5854 on total locomotor activity. The cumulative motor disability scores and locomotor activity counts were determined from the total determined over 15 and 30-min intervals, respectively, for 7 h. Each bar represents the mean ± S.E. ($n = 4$). (D) Time course of the effect of ASP5854 on locomotor activity. Each point represents the mean motor disability score determined over 15 min and the locomotor activity counts determined over 30 min ($n = 4$). (*) $p < 0.05$ and (**) $p < 0.01$ compared with vehicle-treated group ((A and B) Friedman followed by Dunnett's multiple comparisons and (C and D) analysis of variance, based on the randomized block design, followed by Dunnett's multiple comparison test).

tors can decrease the binding affinity of D_2 receptors [13] and alter the release of GABA, acetylcholine, and glutamate within the basal ganglia so that they affect key transmitters involved in the regulation of motor behavior [15,25,31,36]. These data suggest that a functional interaction exists between adenosine A_{2A} receptors and dopamine D_2 receptors that can modulate striatal activity. These antagonistic adenosine–dopamine interactions may be important in the regulation of the activity of the basal ganglia and could explain the depressant and stimulating effects of adenosine A_{2A} receptor agonists and antagonists on motor behavior [12].

In fact, adenosine A_{2A} antagonists can modulate dopamine-mediated behaviors such as haloperidol-induced catalepsy and dopaminergic drug-induced circling behavior in hemi-parkinsonian rats [17,24]. In a non-human primate PD model, the selective adenosine A_{2A} antagonists KW-6002 (istradefylline) and ST1535 improved motor disability [21,37]. Especially, in clinical trials with PD patients, KW-6002 significantly potentiated the antiparkinsonian response by a low dose of levedopa [1] and shortened the time of wearing-off [26]. These findings support the hypothesized role of A_{2A} receptors as neuromodulators of dopaminergic function and suggest that they may play an important role in movement disorders such as PD. As a result, many selective adenosine A_{2A} receptor antagonists have recently been developed (currently in the clinical stages) as drugs intended for the treatment of PD.

5-[5-Amino-3-(4-fluorophenyl)pyrazin-2-yl]-1-isopropylpyridine-2(1*H*)-one (ASP5854) is a novel adenosine A_1 and A_{2A} receptor dual antagonist that was recently identified via our chemical optimization screening of pyrazolopyrimidine derivatives. We have recently shown that the compound reverses adenosine A_{2A} agonist- or haloperidol-induced catalepsy in rodents and potentiates the rotation induced by a subthreshold dose of L-DOPA in hemi-parkinsonian rats [29]. Furthermore, a non-human primate PET study revealed that anti-cataleptic effect of ASP5854 correlated well with the magnitude of adenosine A_{2A} receptor occupancy in the striatum [30]. These results suggest that ASP5854 is a promising candidate for the treatment of PD.

In humans and non-human primates, systemic administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) produces motor disability that closely resembles that seen in idiopathic PD patients. This motor disability is associated with a selective loss of dopaminergic neuronal cells in the pars compacta of the sub-