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BRAIN RESEARCH

Research Report

MP-124, a novel poly(ADP-ribose) polymerase-1 (PARP-1) inhibitor, ameliorates ischemic brain damage in a non-human primate model

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ABSTRACT

Overactivation of poly (ADP-ribose) polymerase-1 (PARP-1) in response to DNA damage is considered to play a crucial role in the development of post-ischemic neuronal injury, such as ischemic stroke. The present study was undertaken to clarify the beneficial effects of MP-124, a novel PARP-1 inhibitor, on neurological deficits and cerebral infarcts following middle cerebral artery occlusion (MCAO) in the monkey. The effects of MP-124 on cerebral infarcts and neurological deficits in monkeys were investigated in permanent MCAO (pMCAO) and transient MCAO (tMCAO) models. In a dose-dependency study, the neurological deficits and cerebral infarct volume were assessed at 28 h after pMCAO. MP-124 significantly reduced the total infarct volume, including that in the cortex/white matter and striatum, at doses of 0.3, 1 and 3 mg/kg/h by 22, 54 and 64%, respectively. In addition, MP-124 at all doses significantly reduced the overall neurological deficits. Such ameliorative effects of MP-124 were observed in female as well as male monkeys. In the therapeutic time window (TTW) study, the neurological deficits and cerebral infarct volume were assessed at several time points after pMCAO or tMCAO. Treatment with MP-124 at 3 and 6 h after MCAO significantly ameliorated not only the neurological deficits but also the infarct volume. MP-124 is thought to exhibit neuroprotective effects with a broad TTW regardless of sex in MCAO models. Such findings suggest that MP-124 may be beneficial for the treatment of acute ischemic stroke.

1. Introduction

Poly (ADP-ribose) polymerase (PARP), an intranuclear enzyme localized in eukaryotic cells, is considered primarily in the human body to protect cells from damage due to the poly (ADP-ribosyl)ation of histone, DNA repair enzymes (DNA polymerase, DNA ligase, DNA topoisomerase, etc.), and further to promote relaxation of the condensed structure of

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Abbreviations: ADP, adenine dinucleotide phosphate; NAD, nicotinamide adenine diucleotide
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chromatin and to facilitate access of DNA repair enzymes to their substrates (Szabo and Dawson, 1998). Activation of PARP simultaneously implies the consumption of its substrate, NAD, and overactivation of PARP results in exhaustion of NAD and further depletion of its source, ATP. These subsequent changes also tend to evoke energy failure of the cell, cell injury and necrosis (Ha and Snyder, 1999). Recent studies have suggested that activation of PARP can induce both necrosis and apoptosis (Yu et al., 2002). This indeed supported the finding that neuronal death was suppressed by treatment with PARP inhibitors in animal models of neurodegenerative diseases, and that damage to neurons by neurotoxins was markedly reduced in PARP knockout animals (Cosi et al., 1996; Mandir et al., 1999). Particularly in situations involving acute neuronal injury, for example, inhibition of PARP is considered to exert neuroprotective effects.

The PARP inhibitors, as tested so far by others, were found to have relatively inadequate enzyme-inhibiting activity, specificity or safety, and could thus not be used for clinical applications (Graziani and Szabo, 2005). We recently identified MP-124, a novel PARP-1 inhibitor with a potent activity displaying a neuroprotective effect in rodent stroke models (Egi et al., in press). In the present study, we demonstrated a reduction in infarct size and in the development of neurological deficits following MP-124 treatment in monkeys subjected to middle cerebral artery occlusion (MCAO) with a broad therapeutic time window (TTW). Furthermore, assessment of sex differences in the effect of MP-124 on the ischemic damage revealed that MP-124 exhibiting ameliorative effects on the MCAO model in female monkeys as well as male monkeys.

2. Results

2.1. *Physiological parameters and pharmacokinetics*

The body temperature and blood gas parameters remained within the normal ranges before MCAO in each group (Table 1). After MP-124 had been continuously administered intravenously at 0.3, 1 and 3 mg/kg/h for 24 h from the start of MCAO, no statistical differences in body weight, body temperature, or blood gas parameters before and after MCAO were evident between the MP-124- and vehicle-treated groups. The concentration at steady state (Css) in plasma at 0.3 and 1 mg/kg/h was 98.1 and 405.5 ng/mL, respectively. The Css in cerebrospinal fluid (CSF) at 1 mg/kg/h was 139.0 ng/mL and the ratio of Css in CSF to plasma was 0.34 (Supplemental Table 1).

2.2. *Dose-dependency*

The dose-dependency of the MP-124 effects on the development of neurological deficits and cerebral infarct volume was investigated in the pMCAO model using male cynomolgus monkeys. After MP-124 had been continuously administered intravenously at 0.3, 1 and 3 mg/kg/h for 24 h from the start of MCAO, the neurological deficits and cerebral infarct volumes on TTC staining were examined at 28 h after pMCAO (Fig. 1A). MP-124 significantly ameliorated the total neurological deficit score at all three doses examined (Fig. 1B), and the effect was dose-dependent ($P=0.002$, Jonckheere's test). Immediately

Table 1 – Body weight and physiological parameters in the pMCAO model.

Group	Time after pMCAO (h)	n	BW (kg)	Physiological parameters				
				BT (°C)	pH	pCO2 (mmHg)	pO2 (mmHg)	pO2 (mmHg)
Vehicle	Pre	10	4.37±0.12	36.9±0.1	7.448±0.011	40.2±1.4	102.0±3.8	98.0±0.3
	1	10		37.3±0.1	7.419±0.013	43.7±2.7	98.5±4.2	97.4±0.3
	6	10		37.9±0.2	7.507±0.011	35.1±0.8	91.6±3.9	97.5±0.3
	24	8		37.0±0.2	7.558±0.013	29.3±1.2	95.3±3.9	98.4±0.3
MP-124 0.3 mg/kg/h	Pre	9	4.43±0.18	36.9±0.1	7.436±0.013	43.0±1.6	106.8±4.6	98.2±0.3
	1	9	($p=0.9822$)	37.2±0.1	7.403±0.014	46.5±2.1	109.0±4.1	98.0±0.3
	6	9		37.7±0.1	7.517±0.012	35.0±1.1	95.4±1.5	98.1±0.2
	24	9		37.1±0.1	7.535±0.011	30.0±0.7	101.8±2.6	98.7±0.2
MP-124 1 mg/kg/h	Pre	9	4.34±0.12	36.9±0.1	7.463±0.016	39.9±1.3	98.2±4.9	97.9±0.3
	1	9	($p=0.9988$)	37.4±0.1	7.445±0.016	41.7±2.4	104.3±5.0	98.1±0.2
	6	9		37.7±0.1	7.507±0.015	36.5±2.0	97.2±3.9	98.2±0.2
	24	9		37.3±0.2	7.548±0.008	30.6±1.2	98.1±2.7	98.4±0.2
MP-124 3 mg/kg/h	Pre	10	4.40±0.17	37.0±0.1	7.428±0.014	40.3±1.7	107.1±4.4	98.3±0.2
	1	10	($p=0.9978$)	37.5±0.2	7.410±0.010	41.5±1.7	101.8±3.3	97.8±0.2
	6	10		37.9±0.2	7.518±0.010	33.4±1.3	93.4±3.2	97.9±0.3
	24	10		37.2±0.2	7.567±0.009	27.9±0.5	102.8±2.8	98.8±0.1
p value	Group			0.6430	0.2489	0.1757	0.2629	0.1140
	Group x time			0.8052	0.3030	0.7176	0.5661	0.5929

There were no statistical differences in body weight (BW) between the MP-124- and vehicle-treated groups using Dunnett's multiple comparison test. The results of repeated measures ANOVA are presented as *p*-values for the factor (group) and factor (group x time), and showed no significant effects.