MEDIMOND - *Monduzzi Editore International Proceedings Division*

XVII International Congress of Neuropathology

ICN

Salzburg (Austria), September 11-15, 2010

XVII[th] International Congress of Neuropathology
2010
SALZBURG * AUSTRIA

www.ICN2010.org

MEDIMOND
INTERNATIONAL PROCEEDINGS

Via G. Verdi 15/1, 40065 Pianoro (Bologna), Italy
www.medimond.com • info@medimond.com

Printed in November 2010 by Editografica • Bologna (Italy)

ISBN 978-88-7587-595-4

monduzzi editore
INTERNATIONAL PROCEEDINGS DIVISION

Index

D-cycloserine reverses recognition deficits in MPTP-induced Parkinson's disease mice model

Huang G. J.[1], Ho S. C.[1], Lai C. K.[2], Gu S. L.[2], Hsieh M. H.[3,4*], Ho Y. J.[1*]

[1] *School of Psychology,* [2] *School of Medical Laboratory and Biotechnology,* [3] *Department of Psychiatry, Chung Shan Medical University Hospital,* [4] *School of Medicine, Chung Shan Medical University, Taiwan, ROC*

Summary

This study investigated behavioral effects of D-cycloserine (DCS) and amantadine (AM) on MPTP-induced Parkinson's disease (PD) mice model. One day after the MPTP lesion, the animals received daily injection of DCS or AM, at the dose of 5 and 10 mg/kg/day. A battery of behavioral test was performed to elucidate motor, cognitive, emotional, and learning function in the mice. MPTP caused a motor impairment, which reversed spontaneously to control levels 10 days after the lesion. However anxiety-like and learning behaviors were not affected by MPTP lesion. Object recognition was suppressed by MPTP, which was ameliorated by the treatment of DCS and AM at the dosage of 10 mg/kg/day. These results suggest that DCS may have beneficial effects on dementia associated with PD.

Introduction

Dementia is observed in a high percentage, 25-30%, of patients with Parkinson's disease (PD), where cognitive impairments in working memory and visuospatial function are the main symptoms. However, development of drug therapy for dementia in PD has been hampered because the pathophysiology is not yet fully understood.

1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is widely used to induce animal models of PD. MPTP causes not only dopaminerergic degeneration but also glutamatergic dysfunction that has been implicated in pathophysiology of PD (Raju et al., 2008) and is suggested to be involved in cognitive impairments in MPTP-lesioned animals (Schneider et al., 2000). Our previous study demonstrated that behavioral deficits observed in MPTP-lesioned rats may be similar to symptoms seen in PD patients with dementia (Sy et al., 2010; Wang et al., 2009a). Therefore, drugs modulating the function of glutamatergic N-methyl-D-aspartate (NMDA) receptors may have beneficial effects on PDD therapy.

Amantadine, an antagonist of NMDA receptors, has been applied in the treatment

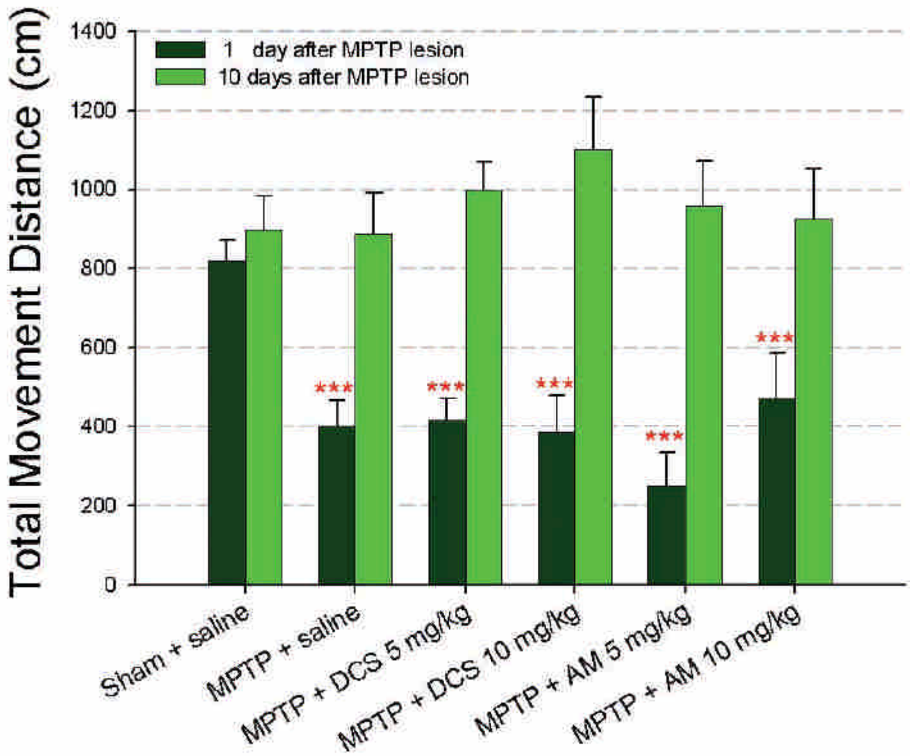

*Fig. 1. Effects of D-cycloserine and amantadine on MPTP-induced motor dysfunction. ***, $P < 0.001$, compared to sham-operated group on day 1.*

of PD. However, because NMDA receptors are involved in a number of important behavioral functions, the use of NMDA receptor antagonists alone is controversial (Rajput, 2006). D-cycloserine (DCS), a partial agonist at the glycine binding site on the NMDA receptor, has been demonstrated to improve cognitive function (Ressler et al., 2004). Accordingly, with the objective of evaluating the potential of DCS on PDD therapy, we examined the effects of DCS on object recognition, emotional, and learning behaviors in mice after MPTP lesion, by using a battery of behavioral tests. Our results showed that DCS treatment improves MPTP-induced deficits in object recognition, suggesting that this drug may have beneficial effects on PDD therapy.

Materials and methods

Male C57BL/6 mice (27±2 g, n = 86; BioLasco Taiwan Co., Ltd) were used. All experimental procedures were approved by the Animal Care Committee of CSMU (IACUC approval No.: 768). The mice were administered with MPTP (20 mg/kg/2 h, 4 injections, i.p.) or saline (1 ml/kg). Starting from one day after MPTP lesion, the mice received daily injections of saline or DCS or AM (5 or 10 mg/kg/day, i.p.) (Sigma, USA). The injection (3 ml/kg) was performed 30 min after the behavior test on that day.

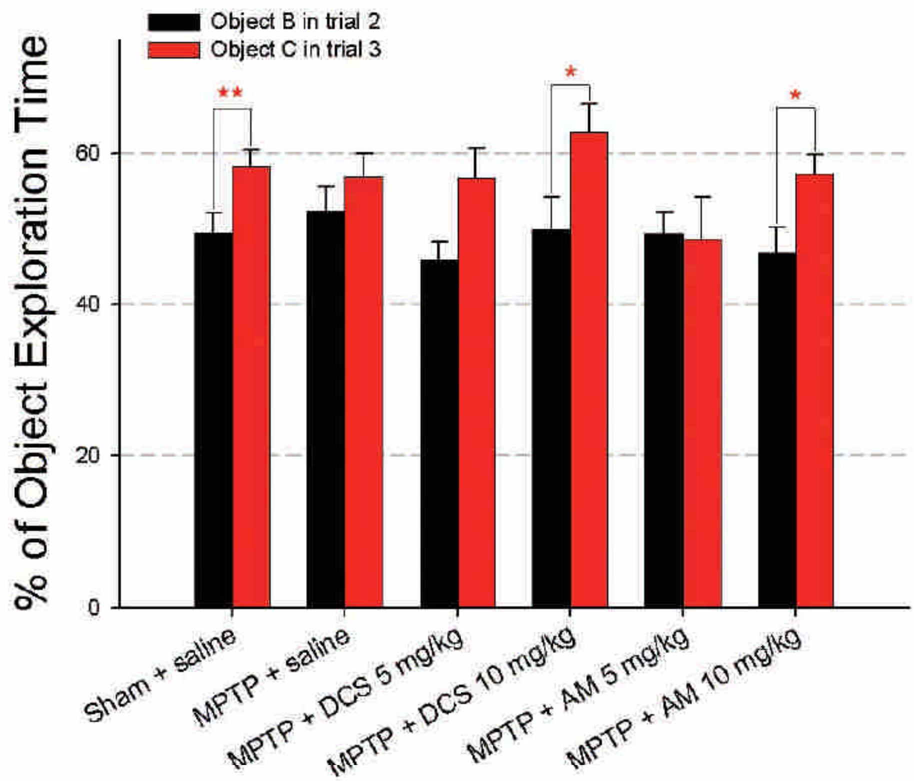

*Fig. 2. Effects of D-cycloserine and amantadine on the behavior of MPTP-lesioned mice in the object recognition test. *, P < 0.05, **, P < 0.01, compared to the exploration time spent on object B in trial 2.*

Behavioral tests: (1) Open field (OF) test: An open field (40×40×60 cm) was used for measuring motor function (5 min), on the 1st and 10th day after MPTP lesion. Total movement distance was recorded. **(2) Object recognition (OR) test:** On the 11th day after MPTP lesion, OR test was performed in a 3-trial session with a 15 min of inter-trial interval. The mouse was placed in a test-cage (40×40×60 cm) with 2 identical objects (for 5 min). In the last (testing) trial, one of the 2 objects was replaced by a new one, and the time spent at each of the objects was recorded. **(3) Elevated plus-maze (EPM) test:** On the 12th day after MPTP lesion, EPM test (5 min) was performed for measuring emotional behaviors. **(4) Active avoidance (AA) test:** On the 13th – 15th days, AA test was performed in a shuttle box (AccuSan, USA) for measuring learning ability (Lee et al., 2008). The mice underwent 50 trials of escapable conditioned stimulus (tone, 80 db)-unconditioned stimulus (electrical shock, 0.3 mA) (CS-UCS) pairings. Each trial began with a 3-second of CS and followed by a 10 sec UCS. The number of avoidances, escapes, and failures were recorded.

Results

(1) OF test: MPTP lesion decreased the total movement distance in the OF test, compared to the control group ($F(9, 117) = 9.339$, $P < 0.05$). The above changes were

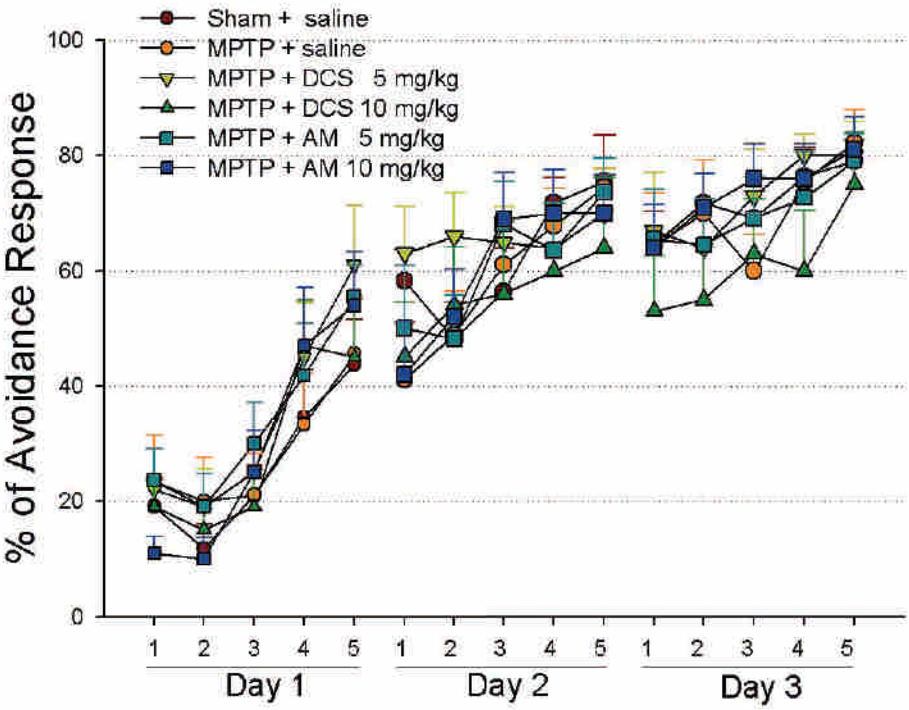

Fig. 3. Effects of D-cycloserine and amantadine on learning behavior in the active avoidance test in MPTP-lesioned mice.

no longer observed 10 days after MPTP lesion (Fig. 1). **(2) OR test:** In the control group, the percentage of time spent on exploring the new object was significantly higher than that spent on the old object (d.f. = 12, t = 3.635, P < 0.01). No such phenomenon was observed in MPTP-lesioned mice (d.f. = 11, t = 1.219, P > 0.05). However, in the mice treated by MPTP and accompanied with DCS and AM, at the dose of 10 mg/kg/day, the percentage of time spent on the new object was significantly higher than that on the old object (d.f. = 11, $t \geqq 2.373$, both P-values < 0.05) (Fig. 2). **(3) EPM test:** The behaviors in the EPM test were not different between sham and MPTP-treated groups (data not shown). **(4) AA test:** ANOVA repeated measure revealed main effect of time on the number of avoidance ($F(14, 770) = 85.522$, P < 0.001). But no drug effect and time-by-drug interactions were observed (Fig. 3).

Conclusions

MPTP treatment disrupted object recognition in mice, but such impairment was blocked by the treatment of DCS and AM at the dosage of 10 mg/kg/day, suggesting that DCS may has beneficial effects on PD.

Our previous study showed that MPTP-lesioned rats present deficits in emotional, learning, and recognition behaviors similar to that observed in patients with dementia (Sy et al., 2010; Wang et al., 2010; Wang et al., 2009). But interestingly, MPTP lesion in mice showed only recognition deficit but not emotional and learning impairments, indicating species differences.

Glutamatergic hyper-activity has been observed after MPTP lesion and is proposed to be involved in pathophysiology of PD. AM, an antagonist of NMDA receptors, is thus being used to treat PD in the clinic. However, the application of AM in PD is still controversial because the NMDA receptors are important for cognitive function (Rajput, 2006). DCS, as a partial agonist, may increase the activity of NMDA receptors and thus improve object recognition in MPTP-lesioned mice. However, AM showed also beneficial effects on object recognition in this study.

Since DCS has been demonstrated improving cognition (Ressler et al., 2004), anxiety-like behavior (Ho et al., 2005; Wu et al., 2008), and increasing episodic-like memory in MPTP-lesioned animals (Wang et al., 2010), this drug may has potential for treatment of dementia associated with PD.

References

Ho, Y.J., Hsu, L.S., Wang, C.F., Hsu, W.Y., Lai, T.J., Hsu, C.C., Tsai, Y.F., 2005. Behavioral effects of D-cycloserine in rats: the role of anxiety level. Brain Res. 1043, 179-85.

Lee, Y.T., Wang, W.F., Cheng, C.W., Wu, S.L., Pawlak, C.R., Ho, Y.J., 2008. Effects of escapable and inescapable stressors on behavior and interleukin-2 in the brain. Neuroreport. 19, 1243-7.

Rajput, A., 2006. Can amantadine therapy delay the onset of dementia in Parkinson's disease? Nat Clin Pract Neurol. 2, 648-9.

Raju, D.V., Ahern, T.H., Shah, D.J., Wright, T.M., Standaert, D.G., Hall, R.A., Smith, Y., 2008. Differential synaptic plasticity of the corticostriatal and thalamostriatal systems in an MPTP-treated monkey model of parkinsonism. Eur J Neurosci. 27, 1647-58.

Ressler, K.J., Rothbaum, B.O., Tannenbaum, L., Anderson, P., Graap, K., Zimand, E., Hodges, L., Davis, M., 2004. Cognitive enhancers as adjuncts to psychotherapy: use of D-cycloserine in phobic individuals to facilitate extinction of fear. Arch Gen Psychiatry. 61, 1136-44.

Schneider, J.S., Tinker, J.P., Van Velson, M., Giardiniere, M., 2000. Effects of the partial glycine agonist D-cycloserine on cognitive functioning in chronic low dose MPTP-treated monkeys. Brain Res. 860, 190-4.

Sy, H.N., Wu, S.L., Wang, W.F., Chen, C.H., Huang, Y.T., Liou, Y.M., Chiou, C.S., Pawlak, C.R., Ho, Y.J., 2010. MPTP-induced dopaminergic degeneration and deficits in object recognition in rats are accompanied by neuroinflammation in the hippocampus. Pharmacol Biochem Behav. 95, 158-65.

Wang, A.L., Liou, Y.M., Pawlak, C.R., Ho, Y.J., 2010. Involvement of NMDA receptors in both MPTP-induced neuroinflammation and deficits in episodic-like memory in Wistar rats. Behav Brain Res. 208, 38-46.

Wang, W.F., Wu, S.L., Liou, Y.M., Wang, A.L., Pawlak, C.R., Ho, Y.J., 2009. MPTP lesion causes neuroinflammation and deficits in object recognition in Wistar rats. Behav Neurosci. 123, 1261-70.

Wu, S.L., Hsu, L.S., Tu, W.T., Wang, W.F., Huang, Y.T., Pawlak, C.R., Ho, Y.J., 2008. Effects of D-cycloserine on the behavior and ERK activity in the amygdala: role of individual anxiety levels. Behav Brain Res. 187, 246-53.