Note

Significant Effect of Dimethylsulfoniopropionate on Parkinson’s Disease of Senescence-Accelerated Mice Induced by 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine

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Summary The induction of Parkinson’s disease (PD) in senescence-accelerated mice (SAMP8) by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and the effects of dimethylsulfoniopropionate (DMSP) on induced PD model mice of SAMP8 were investigated for 5 wk. After many trials, the tail suspension test determining the PD symptoms indicated that an appropriate amount of MPTP clearly raises the SAMP8 mice to the PD-model mice. Moreover, DMSP administration to the PD-SAM model mice proved to completely reduce the PD symptoms in the mice and to accumulate large amounts of norepinephrine, dopamine and dioxyphenylacetate in the mouse brains without cerebellums. These results suggest that catecholamines accumulated in large quantities by the supplementation of DMSP to the double-diseased mice, PD-SAMP8 model mice, completely ameliorated the PD symptoms in these model mice.

Key Words dimethylsulfoniopropionate, Parkinson’s disease, senescence-accelerated mice, catecholamines

A tertiary sulfonium compound, dimethylsulfoniopro- pionate (DMSP), is found in marine animals, especially green sea algae in large amounts (1), and has been customarily ingested in large and small amounts by a number of people in Japan for many years (2). We have examined the effects of DMSP on aquatic and terrestrial animals and obtained a variety of noticeable results (3–9). In contrast, Parkinson’s disease (PD) has proven to principally cause a deficiency in dopamine in the substantia nigra of the brain and sympathetically degenerates and/or degrades the dopaminergic-, norepinephrinergic-, and cholinergic-nervous systems in the brains, resulting in dementia in humans (10–12). However, L-dopa does not completely recover the symptoms of PD (13), although L-dopa is proven to be the most effective among all the drugs used for curing this disease to date (14). We then examined the effects of DMSP on the PD-model mice induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which indicated that addition of DMSP to the PD-model mice induced from C57BL6 mice effectively ameliorates the characteristic PD symptoms of PD-model mice elicited by MPTP (13). We further attempted to examine whether or not MPTP can induce parkinsonism in senescence-accelerated mice (SAM)P8 and whether DMSP exerts any effect on the PD-model mice of SAMP8, whose brains exhibit the characteristic properties of early aging (i.e., loss of learning and memory) (14).

Materials and Methods

DMSP was synthesized and purified to 99.8% purification (from element analysis) (3). 3,4-Di-oxyphenylacetic acid (DOPAC) was obtained from Sigma-Aldrich Co., Ltd., Japan. All other chemicals were of the best available quality (13). The SAMP8 male mice were kindly gifted from emeritus Prof. MD. Takeda T. in Kyoto University. The rearing conditions were the same as those in the previous report (13), except for the following experimental conditions. The twenty mice were divided into two groups, one fed distilled water (the control group) and the other DMSP solution at 5×10−4 M (the DMSP group) for 2 wk. Thereafter, the control and DMSP groups were divided into two groups. One group was further subjected to an intraperitoneal injection of MPTP saline solution (0.5 mL) at 20 mg/kg body wt as a daily dose for 3 consecutive days from the day before the start of the experiment and then at 10 mg/kg body wt only on the first day of every week from the 2nd to the 5th week in the control and DMSP groups with MPTP. The assigned combination of DMSP and MPTP is shown in Table 1. The body weights of mice in the a, b, c and d groups at the start of the experiments were 27.4±1.70, 27.8±1.22, 29.2±0.77 and 28.1±1.25 g.
Table 1. Combination of DMSP and MPTP designed in the experiments.

<table>
<thead>
<tr>
<th>Group</th>
<th>a</th>
<th>b</th>
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<tr>
<td>DMSP</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
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<tr>
<td>MPTP</td>
<td>–</td>
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–, absence; +, presence.

Fig. 1. The frequency of immobility duration of senescence-accelerated mice (SAMP8) in combination of DMSP and MPTP. The DMSP solution (DMSP group) and the distilled solution (control group) were given ad libitum to two groups (ten mice in each) for 2 wk. An appropriate amount of MPTP solution was then intraperitoneally injected into one of the two groups, forming the four groups: a, [DMSP (−)–MPTP (−)]; b, [DMSP (−)–MPTP (+)]; c, [DMSP (+)–MPTP (−)] and d, [DMSP (+)–MPTP (+)]. The immobility duration in the four groups was determined by a new Tail suspension test and expressed in terms of the frequency (total numbers/6 min) (means±SD, n = 5) of immobility duration. The symbols, * and †, show significant differences (p<0.05) from the corresponding start values and the a group at the indicated times. For experimental conditions see details in “Materials and Methods.”

Fig. 2. The frequency of tremor duration of senescence-accelerated mice (SAMP8) in combination of DMSP and MPTP. The DMSP solution (DMSP group) and the distilled solution (control group) were given ad libitum to two groups (ten mice in each) for 2 wk. An appropriate amount of the MPTP solution was then intraperitoneally injected into one of the two groups, forming the four groups: a, [DMSP (−)–MPTP (−)]; b, [DMSP (−)–MPTP (+)]; c, [DMSP (+)–MPTP (−)] and d, [DMSP (+)–MPTP (+)]. The tremor duration in the four groups was determined by a new Tail suspension test and expressed in terms of the frequency (total numbers/6 min) (means±SD, n = 5) of tremor duration. The symbols, * and †, show significant differences (p<0.05) from the corresponding start values and the a group at the indicated times. The experimental conditions were the same as those in Fig. 1.

Results

The frequency of immobility duration and of tremor duration in all the groups was estimated at the start, the 1st and 2nd and the start, the 4th and 5th week, respectively. These results are shown in Figs. 1 and 2. The frequency of immobility and tremor duration in all the test groups was much the same at the start of the experiments. Thereafter, the frequency of immobility and tremor duration in all the groups in the 2nd and 5th week exhibited almost the same trends as that in the 1st and 4th week. The frequency of immobility and tremor duration in the b group proved to be much greater than that in the a group, but the supplementation of DMSP decreased the frequency of immobility and tremor duration in the b group to that in the d group at indicated times. However, the frequency of the immobility and tremor duration in the c group was comparable to that in the d group at indicated times. In contrast, the amounts of norepinephrine, dopamine and DOPAC in the brains without cerebellum of the mice in the c and d groups were estimated in the 5th week. The results are shown in Fig. 3A–C, in which the amounts of norepinephrine (A), dopamine (B) and DOPAC (C) in the d group proved to be significantly higher than those in the c group.
Fig. 3. The amounts of norepinephrine, dopamine and DOPAC in the brains of senescence-accelerated mice (SAMP8) in the control and MPTP groups with DMSP. The amounts of norepinephrine, dopamine and DOPAC in the brains without cerebellum of the mice in the two groups, c. [DMSP (+)–MPTP (−)] and d. [DMSP (+)–MPTP (+)], were estimated in the 5th week. The values are shown in terms of the amounts (μg/g wet wt) (mean±SD, n=5) of norepinephrine, dopamine and DOPAC (A, B and C). The symbol, *, shows significant differences (p<0.01) from the corresponding control values. For experimental conditions see details in "Materials and Methods."

Discussion

After various trials, the supplementation of appropriate amounts of MPTP to the control (no additive) group proved to significantly increase the frequency of immobility duration in the 1st and 2nd week and that of tremor duration in the 4th and 5th week. The facts demonstrate that the administration of MPTP to the SAMP8 raised the diseased mice to the PD-model mice under the experimental conditions. However, the amounts of MPTP and the time which are needed to make the normal SAMP8 into the PD-model mice of the SAM were much larger and later than those of the C57BL6 mice previously tested (13). The discrepancy suggests that it is much more difficult to induce PD by MPTP in SAMP8 mice than in C57BL6 mice. This is probably because the aging (the loss of learning and memory) of SAMP8 at 20 wk of age proceeds fairly well (14, 16) and thus the central nervous system in the mouse brains with substantia nigra is surrounded by larger amounts of amyloid precursor peptide and beta-protein (14, 17). Yet, the preliminary supplementation of DMSP to the MPTP-supplemented group remarkably reduced the frequency of immobility and tremor duration of the MPTP-group to the control group levels. Moreover, the amounts of norepinephrine, dopamine and its derivative, DOPAC, proved to greatly increase in mouse brains without cerebellum from the MPTP and DMSP-supplemented group versus mice from the DMSP-supplemented group in the 5th week.

In our previous experiments, DMSP proved to rapidly incorporate in comparable amounts into the brains and livers of carp (4), rats (8) and mice (9), noticeably activate the mobility and accumulate catecholamines in the viscera of the animals and the PD-model C57BL6 mice (8, 9, 13), markedly recover the loss of learning and memory of SAMP8 (5, 6), and completely ameliorate the PD-model mice of C57BL6 (13). In contrast, there are significant reports that catecholamines promote the synthesis of nerve growth factor (NGF) in the astroglial and fibroblast cells in the mouse central nervous system (18), that NGF releases the amyloid precursor from the nerve model cells, PC12 cells (19), and that DMSP stimulates the outgrowth and elongation of neurites from the PC12 cells (20) and significantly recovers them from the cells inhibited by MPTP (21).

For the reinstatement of the double-lesioned mice, PD-SAMP8 model mice, our findings and the above reports suggest that DMSP rapidly increases the amounts of catecholamines, which restore their deficiencies in the substantia nigra of the brains, and further that increased catecholamines elevate the amounts of NGF, which releases surrounding amyloid proteins from various neurons and promotes the regeneration of neurons in the brains.

However, further detailed experiments are needed to elucidate the ameliorating mechanisms of PD and senile dementia by DMSP.

REFERENCES


5) Nakajima K. 2003. Direct effect of high concentrations


