Estrogen Increases Striatal GDNF Immunoreactivity with no Effect on Striatal FGF-2 Immunoreactivity of MPTP-Treated Mice

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Background: *Glial derived neurotrophic factor (GDNF) and basic fibroblast growth factor (FGF-2) protect nigrostriatal dopaminergic (DA) neurons and their projections in animal models of Parkinson's disease (PD). Recent data indicate neuroprotective effects of estrogen in PD animal models through its anti-inflammatory and anti-oxidative effects, yet the hormonal effects on GDNF and FGF-2 expression in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated mice remain uninvestigated.*

Objective: *To determine the effects of 17 beta-estradiol (E2) on DA innervation and the expression of GDNF and FGF-2 in the striatum of MPTP-treated mice.*

Material and Method: *Adult male mice were treated with E2 or vehicle for 11 days during which they were injected with MPTP or saline on the sixth day. The striatum was collected on day 11 and processed for tyrosine hydroxylase (TH), GDNF, and FGF-2 immunohistochemistry. Extent of DA innervation and the expression of GDNF and FGF-2 in the striatum were assessed by measuring optical density of TH, GDNF, and FGF-2 immunoreactivity, respectively.*

Results: *MPTP induced loss of DA axons and upregulation of FGF-2 expression, but did not alter GDNF level. E2 alleviated loss of DA axons, increased GDNF level, yet caused no change in FGF-2 level of the MPTP-intoxicated animals.*

Conclusion: *One possible mechanism by which E2 protects nigrostriatal DA axons against MPTP is through upregulation of striatal GDNF.*

Keywords: *GDNF, FGF-2, Estrogen, MPTP, Nigrostriatal dopaminergic axon*

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Parkinson's disease (PD) is primarily due to the progressive loss of nigrostriatal dopaminergic (DA) neurons and their projections. Greater prevalence of PD in men compared to women has been reported[1]. Furthermore, estrogen improves motor disability in parkinsonian postmenopausal women with motor fluctuations[2] and reduces the risk of PD in postmenopausal women[3]. Altogether, these data denote beneficial effects of this ovarian hormone in PD. Neuroprotective effects of estrogen is also revealed in PD animal models induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and 6-hydroxydopamine (6-OHDA). This includes protection of nigral DA neurons[4] and striatal dopamine level[5,6].

Glial derived neurotrophic factor (GDNF) has been shown to protect nigral DA neurons and their projections from MPTP[7]. Furthermore, mice with partial deletion of the GDNF receptor, GFR alpha 1, have fewer nigral tyrosine hydroxylase (TH)-immunoreactive (IR) neurons and striatal TH-IR axons and they are more vulnerable to MPTP[8]. Moreover, GDNF increases survival of ventral mesencephalic grafts transplanted into the striatum of 6-OHDA-lesioned rats[9].

Basic fibroblast growth factor (FGF-2) protects cultured mesencephalic DA neurons against MPTP[10] and attenuates loss of striatal DA fibers and nigral DA neurons in MPTP-treated rodents[11]. Also, 6-OHDA-induced reduction of nigral DA neurons is significantly greater in FGF-2-deleted mice compared to the respective wild types, while FGF-2 overexpressing mice have lesser DA neuronal death compared to wild types[10].

Effects of estrogen on GDNF and FGF-2 expression have been reported. The hormone increases GDNF protein in midbrain neuron-astrocyte cultures[12]. In addition, conjugated equine estrogen increases the number of GDNF-IR cells in the peri-ischemic areas of

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the rat hippocampus[13]. In contrast to the effects on GDNF, estrogen deficiency leads to the increased number of FGF-2-IR glia in the ventral tegmental area and these high levels are decreased after estrogen treatment[14]. Furthermore, increased expression of astrocytic FGF-2 in the substantia nigra of 6-OHDA-lesioned male rats is greater than that in 6-OHDA-lesioned female rats[15]. So far, the in vivo effects of estrogen on GDNF and FGF-2 expression in MPTP mouse model of PD have not been demonstrated. To address this issue, the present study examined the effects of 17 beta-estradiol (E2) on DA innervation and GDNF and FGF-2 immunoreactivity in the striatum of MPTP-treated male mice.

Material and Method

Animals

Sixteen male C57Bl/6 mice at the age of 14 weeks were obtained from National Laboratory Animal Center, Thailand. They were housed two to three per cage with a 12-h light-dark cycle at a room temperature of 23°C and had access to food and water ad libitum. All experiments were performed using protocols approved by the Committee of Animal Used for Research of the Faculty of Medicine, Srinakharinwirot University.

MPTP lesion model and E2 administration

Mice were distributed in groups of four to six animals (control group, n = 4; MPTP-treated group, n = 6; MPTP/E2-treated group, n = 6). Animals were treated twice daily with a subcutaneous injection of E2 (Sigma-Aldrich, St. Louis, MO) at 2 μg day^{-1} or vehicle (0.1 ml of 0.9% saline containing 1% gelatin and 1% ethanol) for 11 days. On day 6, mice received four intraperitoneal injections of MPTP-HCl (4x15 mg/kg of free base; Sigma-Aldrich) dissolved in sterile 0.9% saline at 2-h interval in 1 day. Control animals received four intraperitoneal injections of 0.9% saline.

Immunohistochemistry

All mice were killed by an overdose of pentobarbital sodium (350 mg/kg, intraperitoneal, Sanofi) and perfused transcardially with ice-cold heparinized 0.1 M phosphate buffer saline, pH 7.4 (PBS), followed by chilled 4% paraformaldehyde (Sigma-Aldrich) in 0.1M phosphate buffer, pH 7.4. The brains were post-fixed in the same fixative for 18 h at 4°C and then cryoprotected with 30% sucrose in PBS at 4°C until the brains sank. A 1:10 series of thirty five-micrometer coronal sections were cut through the striatum, using a cryostat (Leica CM 1850, Wetzlar). The sections were stored free-floating at -20°C in cryo-protectant until used.

For tyrosine hydroxylase (TH), GDNF, and FGF-2 immunohistochemistry, sections were rinsed in PBS to remove any cryoprotectant, then blocked for endogenous peroxidase activity with 50% methanol containing 0.3% H_2O_2. After 30 min incubation in blocking buffer (PBS containing 0.3% triton X-100 and 10% normal goat serum) to reduce non-specific binding, sections were rinsed in PBS, then incubated overnight at room temperature with anti-TH antibody (a marker for DA neurons, 1:3,000, rabbit polyclonal, Chemicon, Millipore Corp., Billerica, MA), anti-GDNF (1:100, rabbit polyclonal, Santa Cruz Biotechnology, CA), and anti-FGF-2 (1:100, rabbit polyclonal, Santa Cruz Biotechnology). This was followed by incubation in biotinylated goat anti-rabbit IgG (1:400 for TH staining, 1:300 for GDNF and FGF-2 staining, Vector Laboratories, Burlingame, CA) at room temperature and subsequently in avidin peroxidase (1:5,000, Sigma-Aldrich). Immuno-reactivity was visualized with cobalt and nickel-intensified 3, 3'-diaminobenzidine tetrahydrochloride (Sigma-Aldrich)/H_2O_2. PBS rinses (5 min x 3) were performed between each step. Finally, sections were mounted onto slides, dehydrated, and coverslipped. Negative control study was performed by omission of the primary antibody.

Quantification of TH, GDNF, and FGF-2 immuno-reactivity in the striatum

The extent of DA innervation and the expression of GDNF and FGF-2 protein in the striatum was assessed by measuring the optical density (OD) of TH, GDNF, and FGF-2 immunoreactivity, respectively, in 9-12 sections spanning the striatum with Leica image processing and analysis software (Leica Image Processing Solution Ltd., Cambridge, UK). To correct for variability in lighting conditions, all images were photographed under identical conditions. Background levels were captured from the corpus callosum (for TH quantification) or cerebral cortex (for GDNF and FGF-2 quantification) in each section and subtracted from the total OD measurement. The OD value of each animal was the average OD from each of the nine to twelve measured sections. All analyses were performed in a blinded fashion.

Statistical analysis

All values were expressed as mean $\pm$ SEM. Statistical analysis was carried out using one-way

ANOVA with Student-Newman-Keuls *post hoc* tests. In the present study significance was set at $p<0.05$.

Results

Estrogen attenuates MPTP-mediated loss of striatal TH-IR axons

Following MPTP administration, striatal TH-IR axons diminished extensively such that the OD of TH immunoreactivity was significantly reduced by 59% as compared to control ($p<0.05$) (Fig. 1A-C). In contrast, E2 pretreatment significantly alleviated loss of striatal TH-IR fibers in MPTP-treated mice and the decrease of TH immunoreactivity was reduced from 59% to 46% ($p<0.05$) (Fig. 1A and 1D).

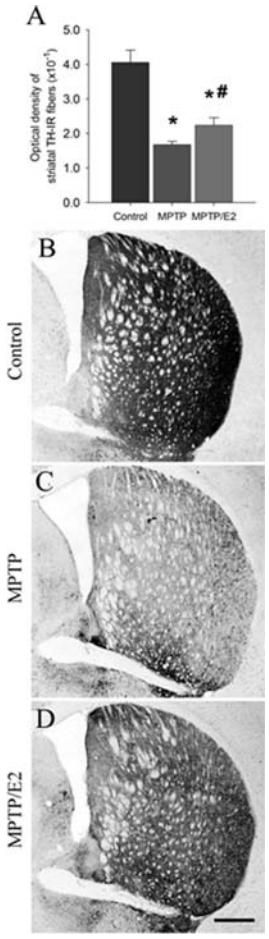

Fig. 1 E2 pretreatment partially protects striatal TH-IR axons against MPTP. (A), Histogram showing the optical density of TH immunoreactivity in the striatum of control animals and MPTP- and MPTP/E2-treated animals on day 5 post-MPTP. (B-D): Representative photomicrographs of striatal sections immunostained for TH of control (B), MPTP-treated animals (C), and MPTP/E2-treated animals (D). Graphed data represent mean ± SEM for four to six animals per group. *Indicates significant difference from control animals, $p<0.05$. #Indicates significant difference from MPTP-treated animals, $p<0.05$. Scale bar in panel D represents a length of 500 μm for panels B-D.

Estrogen significantly increases striatal GDNF expression of MPTP-treated mice

MPTP slightly increased the OD of striatal GDNF immunoreactivity to 106% of control (Fig. 2A-C). E2 significantly upregulated GDNF immunoreactivity in the striatum of MPTP-treated mice to 133% of control ($p<0.05$) (Fig. 2A and 2D). In all animal groups, GDNF immunoreactivity was mainly localized in striatal neurons (Fig. 2B-D).

MPTP-induced upregulation of striatal FGF-2 protein is not altered by E2 pretreatment

Striatal FGF-2 immunoreactivity increased to 160% of control following MPTP intoxication ($p<0.05$) (Fig. 3A-C). In MPTP/E2-treated group, FGF-2 expression was further elevated, yet insignificantly different from MPTP group, to 171% of control (Fig. 3A and 3D). In all animal groups, the majority of FGF-2-IR cells were striatal neurons (Fig. 3B-D). Small numbers of FGF-2-IR glial profiles were observed in the striatum of control animals (Fig. 3B). A marked increase in the number and morphological transformations of FGF-2-IR glial profiles were observed in MPTP-treated mice (Fig. 3C and 3G). E2 pretreatment reduced the number of FGF-2-IR glia in the striatum of MPTP-treated mice (Fig. 3D), but the hormone had no effect on MPTP-induced morphological changes of FGF-2-IR glia (Fig. 3H).

Discussion

The present study shows that in addition to protection of striatal TH-IR axons, E2 also increased striatal expression of GDNF protein in male mice treated with MPTP. The hormone, however, had no effect on increased expression of striatal FGF-2 protein triggered by MPTP.

Our results showing that E2 reduced loss of striatal DA axons in MPTP-treated mice further support previous studies in PD animal models[16]. E2 does not affect the brain level of 1-methyl-4-phenylpyridinium ion[6], which is the major metabolite of MPTP and responsible for the neurotoxic effect of the toxin. In addition, E2 does not alter striatal dopamine and its metabolites in intact male mice[17]. Therefore, increased

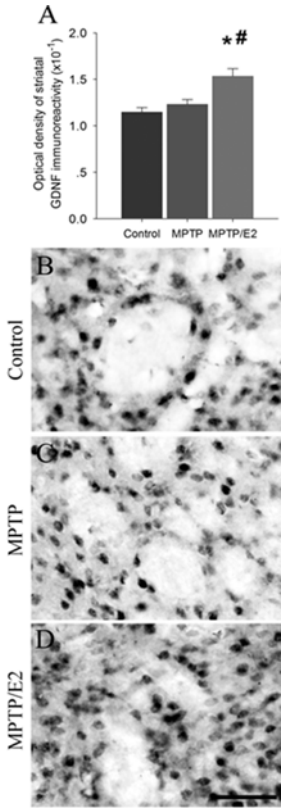

Fig. 2 E2 pretreatment upregulates striatal GDNF immunoreactivity of MPTP-lesioned mice. (A), Histogram showing the optical density of GDNF immunoreactivity of control animals and MPTP- and MPTP/E2-treated animals on day 5 post-MPTP. (B-D), Representative photomicrographs of GDNF-IR cells in the striatum of control animals (B), MPTP-treated animals (C) and MPTP/E2-treated animals (D). All values are mean ± SEM for four to six animals per group. * Indicates significant difference from control animals, $p<0.05$. # Indicates significant difference from MPTP-treated animals, $p<0.05$. Scale bar in panel D represents a length of 50 μm for panels B-D.

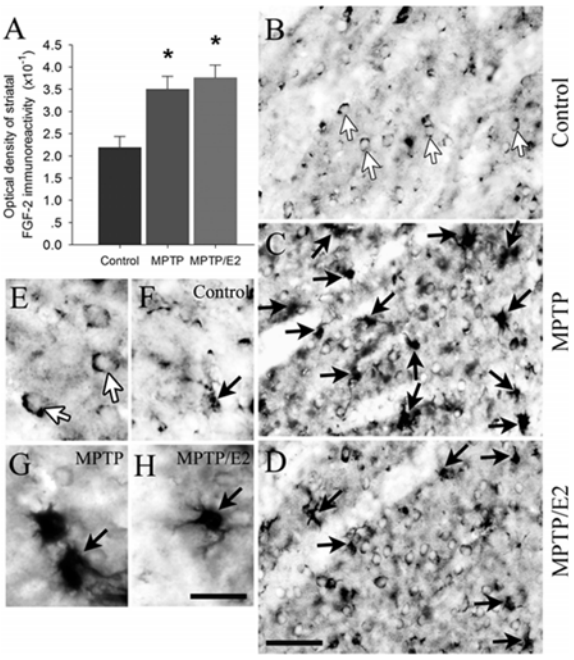

Fig. 3 E2 pretreatment has no effect on MPTP-mediated striatal FGF-2 upregulation. (A), Histogram showing the optical density of FGF-2 immun reactivity of control animals and MPTP- and MPTP/E2-treated animals on day 5 post-MPTP. (B-D), Representative photomicrographs of FGF-2-IR cells in the striatum of control animals (B), MPTP-treated animals (C) and MPTP/E2-treated animals (D). (E-H), White and black arrows point to FGF-2-IR neurons and FGF-2-IR glia, respectively. Higher magnification of FGF-2-IR cells in the striatum of controls (E-F), MPTP-treated animals (G), and MPTP/E2-treated animals (H). All values are mean ± SEM for four to six animals per group. * Indicates significant difference from control animals, $p<0.05$. Scale bar in panel D represents a length of 50 μm for panels B-D and scale bar in panel H represents a length of 25 μm for panels E-H.

striatal dopamine in MPTP/E2-treated mice[6,17] may occur, at least in part, via protection of striatal DA axons. This neuroprotection could be one of the mechanisms underlying a greater prevalence of PD in men than in women[1] and motor disability improvement in parkinsonian postmenopausal women receiving estrogen[2].

Loss of striatal DA axons was associated with increased expression of FGF-2 in the striatum. Since FGF-2 exerts neurotrophic activity on nigrostriatal DA neurons[10], increased FGF-2 may play a role in protection of DA axons against MPTP in an attempt to restore striatal DA innervation. This suggestion is supported by evidence showing a greater number of nigral DA neurons surviving 6-OHDA toxin in wild-type mice compared with those in FGF-2 knockout mice[10].

In contrast to FGF-2, MPTP-provoked DA denervation in the striatum induced no change in GDNF expression. This is in agreement with previous study in MPTP-lesioned animals[18]. One possible explanation for the unresponsive GDNF expression to MPTP toxin

could be that the neurotoxin reduces striatal glutamate[19], whose activation enhances striatal GDNF[20]. This, consequently, may lead to an unchanged GDNF level despite injury of striatal DA axons.

An increase in striatal GDNF of MPTP/E2-treated mice was coincided with reduced loss of striatal TH-IR axons, implying that the hormone may provide neuroprotective effects on nigrostriatal DA axons, at least in part, via GDNF upregulation. This suggestion is supported by in vitro study illustrating that GDNF neutralization abolishes E2 neuroprotective effects against 6-OHDA toxicity[12].

Hyperplasia, hypertrophy, and increased FGF-2 expression of striatal glia are observed in MPTP-lesioned mice[4,21]. These cellular changes may be triggered by products released from damaged neurons and terminals[22]. Consistent with this suggestion, data from MPTP/E2-treated mice have revealed lesser DA denervation and a decreased number of activated glia[4] and FGF-2-IR glia (the present study) compared to MPTP-treated mice. Reduced number of FGF-2-IR glia in MPTP/E2 may also be a direct effect of E2 on striatal glia as estrogen inhibits activation of cultured microglia[23] and astrocytes in injured brain[24]. Furthermore, this hormone can reduce the production of several molecules from reactive glia[23] and decreases glial expression of FGF-2 in intact brain[14].

Striatal FGF-2 immunoreactivity of MPTP/E2 mice was not different from MPTP-treated mice despite less FGF-2-IR glia compared with MPTP-treated mice. In view of previous evidence showing that estrogen upregulates FGF-2 content in pituitary folliculostellate cells[25], E2 may increase the number of FGF-2-IR neurons in the striatum, thereby counteracting a decrease in FGF-2-IR and leading to an unchanged FGF-2 immuno-reactivity in MPTP/E2-treated mice compared with MPTP-treated mice. Further study using the optical fractionator method to estimate the total number of FGF-2-IR neurons and FGF-2-IR glia in the striatum of MPTP and MPTP/E2 mice is required to verify this notion.

Conclusion

The present study demonstrates that E2 pretreatment reduced loss of TH-IR axons, upregulated GDNF immunoreactivity, but had no effect on increased FGF-2 expression in the striatum of MPTP-treated male mice. The results suggest that E2 may, at least in part, protect striatal TH-IR axons against MPTP toxin through upregulation of striatal GDNF.

What is already known on this topic ?

Estrogen increases GDNF expression in vitro (the hormone increases GDNF expression in hypothalamic cell cultures and midbrain neuron-astrocyte cultures), in uninjured brain (estrogen increases GDNF protein levels in the substantia nigra pars compacta and striatum), and in injured brain (the hormone increases the number of GDNF-IR cell in the peri-ischemic areas of the rat hippocampus). So far, there is no study investigating the effect of estrogen on striatal GDNF in MPTP-treated mice.

Estrogen suppresses FGF-2 expression in uninjured brain (estrogen deficiency leads to the increased number of FGF-2-IR glia in the ventral tegmental area and the entorhinal cortex and these high levels are decreased after estrogen treatment) and in injured brain (6-OHDA-lesioned male rats have greater increased expression of astrocytic FGF-2 in the substantia nigra pars compacta than that in female rats). Until now, there is no study investigating the effect of estrogen on striatal FGF-2 in MPTP-treated mice.

What this study adds ?

This study has revealed new evidence regarding the effect of estrogen on the expression of GDNF and FGF-2 protein in the striatum of MPTP-treated mice. The results show that estrogen increased striatal GDNF immunoreactivity. However, there was no change in striatal FGF-2 immunoreactivity in the MPTP-intoxicated mice.

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Potential conflicts of interest

The present study was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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เอสโตรเจนเพิ่ม GDNF immunoreactivity แต่ไม่มีผลต่อ FGF-2 immunoreactivity ในสมองส่วน striatum ของหนูไมซ์ที่ได้รับสาร MPTP

วนิดา ไตรพาณิชย์กุล, เอมอร เจริญสรรพพืช

ภูมิหลัง: *Glial derived neurotrophic factor (GDNF) และ basic fibroblast growth factor (FGF-2) เป็นโมเลกุลที่ออกฤทธิ์ปกป้องเซลล์ประสาทโดปามีนในสมองส่วน substantia nigra pars compacta (SNpc) และ dopaminergic (DA) axons ของเซลล์ประสาทนี้ในสมองส่วน striatum ของสัตว์ทดลองแบบจำลองของโรคพาร์คินสัน หลักฐานจากงานวิจัยบ่งชี้ว่าฮอร์โมนเอสโตรเจนออกฤทธิ์ neuroprotection ในสัตว์ทดลองแบบจำลองของโรคพาร์คินสันโดยต้านการอักเสบและต้านสภาวะ oxidative stress แต่ยังไม่มีรายงานผลของฮอร์โมนนี้ต่อระดับของ GDNF และ FGF-2 ในหนูไมซ์ที่ถูกเหนี่ยวนำให้เกิดภาวะพาร์คินสัน (parkinsonism) โดยสารพิษ MPTP*

วัตถุประสงค์: *เพื่อศึกษาผลของฮอร์โมนเอสโตรเจนต่อปริมาณของ DA axons และระดับของ GDNF และ FGF-2 ในสมองส่วน striatum ของหนูไมซ์ที่ได้รับสาร MPTP*

วัสดุและวิธีการ: *หนูโตเต็มวัยเพศผู้ได้รับ 17 beta-estradiol (E2) หรือ vehicle (ตัวทำละลาย) เป็นเวลานาน 11 วัน หลังจากได้รับ E2 หรือ vehicle 5 วัน สัตว์ทดลองจะได้รับ MPTP หรือ saline ในวันที่ 6 จากนั้นสมองส่วน striatum ของสัตว์ทดลองจะถูกเก็บในวันที่ 11 และนำมาผ่านการย้อม tyrosine hydroxylase, GDNF และ FGF-2 immunohistochemistry*

ผลการศึกษา: *สาร MPTP ลดปริมาณของ DA axons และเพิ่มระดับของ FGF-2 แต่ไม่มีผลต่อระดับของ GDNF ในสมองส่วน striatum ของหนูไมซ์ ฮอร์โมนเอสโตรเจนช่วยปกป้อง DA axons จากสาร MPTP, ไม่มีผลต่อระดับของ FGF-2, และเพิ่มระดับของ GDNF ในสมองส่วน striatum ของหนูไมซ์ที่ได้รับสาร MPTP*

สรุป: *กลไกหนึ่งที่ฮอร์โมนเอสโตรเจนออกฤทธิ์ปกป้อง DA axons ในสมองส่วน striatum จากสารพิษ MPTP คือการเพิ่มระดับของ GDNF ในสมองส่วนดังกล่าว*