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Glutathione peroxidase-1 overexpressing transgenic mice are protected from cocaine-induced drug dependence

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ABSTRACT

Converging evidence has demonstrated that oxidative burdens are associated with drug dependence induced by psychostimulants. Here, we investigated whether oxidative stress directly mediates conditioned place preference and behavioral sensitization (drug dependence) induced by cocaine and whether glutathione peroxidase-1 (GPx-1), a major GPx, modulates cocaine-induced psychotoxic changes in mice. Cocaine-induced drug dependence was followed by increases in c-Fos-immunoreactivity (c-Fos-IR) in the nucleus accumbens. Simultaneously, cocaine significantly increased oxidative parameters and nuclear factor κB (NFκB) activity (i.e. nuclear translocation and DNA binding activity) in the striatum (including nucleus accumbens). Genetic depletion of GPx-1 made mice susceptible to drug dependence induced by cocaine in mice, while genetic overexpression of GPx-1 protected the mice from drug dependence. Pyrrolidine dithiocarbamate (PDTC), a NFκB inhibitor, significantly attenuated the sensitivity induced by the genetic depletion of GPx-1 in mice. However, PDTC did not exhibit any additive effects against the protection afforded by the genetic overexpression of GPx-1. Our results suggest that drug dependence induced by cocaine requires oxidative stress and NFκB activation, and that the GPx-1 gene is a potential protective factor against cocaine-induced drug dependence through positive modulation of NFκB.

1. Introduction

We have recently demonstrated that the major antioxidant enzyme glutathione peroxidase-1 (GPx-1) gene possesses protective potentials against memory impairments and drug dependence induced by methamphetamine (MA) (Mai et al., 2018c, 2018d; Shin et al., 2017; Tran et al., 2017, 2018b), suggesting that oxidative stress mediates MA-induced psychotoxic response. Indeed, Walker et al. (2014) demonstrated that both the cocaine-dependent and MA-dependent participants in the clinical trial showed a significantly decreased total antioxidant capacity (TAC) compared with the controls. Although respective human data are lacking, it is known that cocaine abuse leads to elevated oxidative stress and thereby enhanced proinflammatory status in drug-abusing patients (Fox et al., 2012).

Consistently, evidence associating the harmful outcome of cocaine toxicity with oxidative stress has accumulated during the last decade, and it is believed to play a major role in the negative consequences of cocaine intake. Moreover, cocaine exposure has also been linked to reduced non-enzymatic antioxidant levels, including reduced glutathione (GSH), resulting in elevated reactive oxygen species (ROS), and damaged brain function (Muriach et al., 2010). Furthermore, Uys et al. (2011) demonstrated that increased oxidative stress following cocaine exposure contributes to cocaine-induced behaviors via modulation of glutathione redox status. This demonstration prompt to us to investigate the role of GPx-1 in the current experimental condition.

Accumulating evidence suggests that nuclear factor kappaB (NFκB) transcription factor is a critical molecular target for drug dependence (Ang et al., 2001; Nennig and Schank, 2017; Zhang et al., 2011). In

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particular, it is well-recognized that functional activity of NFκB is up-regulated by repeated cocaine treatment (Ang et al., 2001; Russo et al., 2009). Similarly, morphine and other μ-opioid receptor agonists increase NFκB function *in vitro* (Sawaya et al., 2009; Wang et al., 2004), and regulate NFκB phosphorylation (Zhang et al., 2011). Consistently, pyrrolidine dithiocarbamate (PDTC), a NFκB inhibitor attenuated drug dependence induced by cocaine or morphine (Russo et al., 2009; Zhang et al., 2011).

In this study, we investigated whether conditioned place preference (CPP) and behavioral sensitization (drug dependence) induced by cocaine produce oxidative burdens, whether oxidative stress responsible transcription factor NFκB plays a role as a mediator of the drug dependence induced by cocaine, and whether GPx-1 gene modulates this drug dependence.

Here, we propose that cocaine-induced drug dependence leads to oxidative damage, and that GPx-1 gene acts as a protective modulator against cocaine-induced drug dependence by inhibiting modulation of NFκB signaling.

2. Materials and methods

2.1. Animal

The handling of animals was performed according to the National Institutes of Health (NIH) Public Health Service Policy on Humane Care and Use of Laboratory Animals (2015 Edition; grants.nih.gov/grants/olaw/references/PHSPolicyLabAnimals.pdf) and Institute for Laboratory Animal Research Guidelines for the Care and Use of Laboratory Animals (8th Edition; grants.nih.gov/grants/olaw/Guide-for-the-care-and-use-of-laboratory-animals.pdf). Mice were preserved in a 12 h/12 h light/dark cycle and fed *ad libitum*. GPx-1 knockout (KO) mice were derived from C57BL/6 × 129/SVJ mice as previously described (Ho et al., 1997; Mai et al., 2018b). The breeding pairs of GPx-1 knockout (KO) mice were kindly provided by Professor Ye-Shih Ho (Wayne State University, Detroit, MI, USA). The coding sequence of the GPx-1 gene was disrupted by insertion of a neomycin resistance gene cassette (neo) in the exon 2 in this mouse strain. Breeding pairs of GPx-1 overexpressing transgenic (GPx-1 TG) mice were kindly provided by Professor Xin Gen Lei (Department of Animal Science, Cornell University, Ithaca, New York, U.S.A.). The GPx-1 TG mice were derived from B6C3 (C57BL/6 × C3H) hybrid mice, and have three copies of the GPx-1 transgene (Cheng et al., 1997; Xiong et al., 2004).

Characterization using DNA template extracted from mouse tail was performed by polymerase chain reaction (PCR) analysis. Primer sequences (Bioneer Corporation, Daejeon, Republic of Korea) used for characterization were obtained from previous studies (Mai et al., 2016; Shin et al., 2018).

2.2. Drugs

Cocaine (15 mg/kg, i.p.; Macfarlan Smith Ltd., Edinburgh, UK) was liquefied in saline before use. In order to examine the role of NFκB, mice received pyrrolidine dithiocarbamate (PDTC; 50 mg/kg, i.p.; Sigma-Aldrich, St. Louis, MO, USA), a selective NFκB inhibitor, 1 h prior to every cocaine administration. PDTC was liquefied in saline before use (Shin et al., 2004a). The doses of the drugs were established in our previous studies (Shin et al., 2011, 2018).

2.3. Conditioned place preference (CPP)

The CPP apparatus and procedure were described before (Shin et al., 2009, 2011). For the control group, mice were administrated saline before placing in both compartments. While, mice received cocaine (15 mg/kg, i.p.) before entering the white compartment (Fig. 1). The differences between the time spent in the posttest (day 3) and pretest (day 15) periods were calculated and presented as seconds, indicating the place preference. The period of time for CPP was between 0900 and 1700 h.

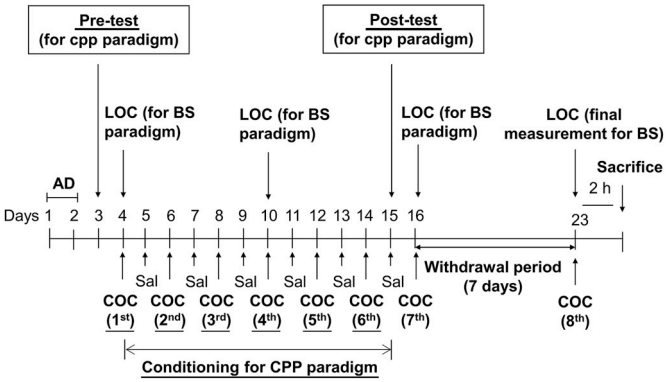

Fig. 1. Experimental schedule for understanding on the role of glutathione peroxidase-1 (GPx-1) in response to conditioned place preference (CPP) and behavioral sensitization (BS) induced by cocaine in mice. For the CPP paradigm, mice received cocaine (15 mg/kg, i.p.) 7 times every other day. For the BS paradigm, mice received final (8th) cocaine (15 mg/kg, i.p.) after the withdrawal period (7 d) post-CPP paradigm. A NFκB inhibitor, PDTC (50 mg/kg, i.p.) was administered 1 h prior to each cocaine injection. AD = adaptation. COC = cocaine. Sal = saline. LOC = locomotor activity.

2.4. Behavioral sensitization

Under typical experimental conditions (Fig. 1), mice received cocaine seven times (on day 4, 6, 8, 10, 12, 14, and 16) followed by a withdrawal period for 7 days, before receiving the final dose of cocaine (8th dose, day 23). Every locomotor activity (LOC) was recorded for a monitoring period of 30 min using an automated video-tracking system (Noldus Information Technology, Wageningen, The Netherlands). An IBM computer operated eight test boxes (40 × 40 × 30 cm high). Mice were sacrificed 2 h after the behavioral sensitization measurement (Mai et al., 2018c; Shin et al., 2009).

2.5. ROS formation measurement

ROS formation was determined by the measurement of the conversion from 2′,7′-dichlorofluorescin diacetate (DCFH-DA) to dichlorofluorescin (DCF) (Nguyen et al., 2018). Striatal homogenates (including nucleus accumbens) were mixed with 2 mL of phosphate-buffered saline (PBS) and 10 nmol of DCFH-DA in methanol. After incubation for 3 h at 37 °C, the mixture was measured at 480 nm excitation and 525 nm emission (Dang et al., 2018b).

2.6. 4-Hydroxynonenal (HNE) measurement

The assessment of the level of lipid peroxidation followed the instructions of the manufacturer, which was described before [OxiSelect™ HNE adduct ELISA kit (Cell Biolabs, Inc., San Diego, CA, USA)] (Dang et al., 2018a; Nguyen et al., 2018). The mixture was measured at 450 nm (Molecular Devices Inc.) and calculated according to the standard curve (Dang et al., 2018a; Nguyen et al., 2018).

2.7. Protein carbonyl measurement

Protein carbonyl determination based on the amount of protein carbonyl groups, which were assessed spectrophotometrically with 2,4-dinitrophenylhydrazine (DNPH)-labeling procedure (Nguyen et al., 2018; Oliver et al., 1987), and measured at 370 nm. The results were divided according to the protein concentration using BCA protein assay reagent (Thermo Scientific, Rockford, IL, USA), and expressed as nmol/mg protein.

2.8. Cytosolic and nuclear NFκB

The procedure of cytosolic and nuclear extraction using NE-PER nuclear and cytoplasmic extraction kit (Thermo Scientific, Rockford, IL) was carried out as previously described (Tran et al., 2012, 2018a). Primary antibody NFκB p65 subunit antibody (65 kDa; 1:1000; sc-372, Santa Cruz Biotechnology, Santa Cruz, CA) was used to detect the NFκB. The intensity of NFκB in the cytosolic and nuclear fractions were normalized to the intensity of matrix p84 antibody (ab487, 1:2000; Abcam, Cambridge, MA) or β-actin antibody (1:300,000; Sigma-Aldrich), respectively.

2.9. DNA binding activity assay

The extraction of nuclear fraction was carried out using *a* nuclear extraction kit (#40410; Active Motif, Carlsbad, California) according to the manufacturer's instructions (Shin et al., 2018).

The DNA binding activities of NFκB p65 were determined by using TransAM® NFκB transcription factor ELISA kit (Active Motif) according to the manufacturer's instructions. Briefly, the wells coated with oligonucleotides containing the NFκB consensus binding site (5' -GGGAC TTTCC-3′) and 20 μg of nuclear protein extract were incubated at room temperature for 1 h. Primary antibody against NFκB p65 subunit and horseradish peroxidase (HRP)-conjugated secondary anti-rabbit IgG were added to the mixture and incubated for 1 h. The mixture was measured at 450 nm using a microplate reader (Molecular Devices, Sunnyvale, CA, U.S.A.) (Shin et al., 2018).

2.10. Western blot analysis

After homogenizing with lysis buffer, containing 200 mM Tris–HCl (pH 6.8), 10% SDS, 5 mM ethylene glycol tetra-acetic acid (EGTA), 5 mM ethylenediaminetetraacetic acid (EDTA), 10% glycerol, and protease inhibitor cocktail (Sigma-Alrich), striatal lysate was centrifuged for 30 min at 13,000 × *g*. The supernatant used for analyzing proteins by western blot as previously described (Mai et al., 2018a). The primary antibodies and HRP-conjugated secondary antibody used were β-actin (42 kDa, 1:300000 dilution; Sigma-Alrich), or GPx-1 (23 kDa, 1:1000; R&D Systems, Minneapolis, MN, USA); and anti-mouse IgG (1:5000; Sigma-Alrich), or anti-goat IgG (1:5000; Sigma-Alrich), respectively. Finally, the membranes were detected using an enhanced chemiluminescence system (ECL Plus®, GE Healthcare, Arlington Heights, IL, USA). The intensity of the bands was measured by Photo-Capt MW (version 10.01 for Windows; Vilber Lourmat, Marne la Vallee, France) and normalized to the intensity of the housekeeping gene (β-actin) (Mai et al., 2018e; Shin et al., 2014).

2.11. Immunocytochemistry

The procedures of perfusion and brain storage were carried as previously described (Mai et al., 2018c). Smaples of brains were sectioned into 35-μm and blocked with 0.3% hydrogen peroxide/PBS and 0.4% Triton X-100 plus 1% normal serum/PBS for 30 min and 20 min, respectively. c-Fos (1:5000; ABE457, Merck Millipore, Billerica, MA, U.S.A.) was used as a primary antibody. After incubating with c-Fos antibody for 24 h, the sections were immersed in biotinylated secondary antibodies (1:1000; Vector Laboratories, Burlingame, CA, USA) for 1 h. Next, sections were incubated with avidin–biotin-peroxidase complex (Vector Laboratories) for 1 h and detected by 3,3′-diaminobenzidine (DAB; Sigma-Aldrich). An Olympus microscope (BX51, Olympus, Tokyo, Japan) with a digital microscope camera (DP72, Olympus) and an IBM PC (Armonk, NY, USA) at 200 × magnification was used to take the digital images. ImageJ version 1.47v software (NIH) was employed to analyze the positive c-Fos-immunoreactivity cells (Mai et al., 2018c; Shin et al., 2018).

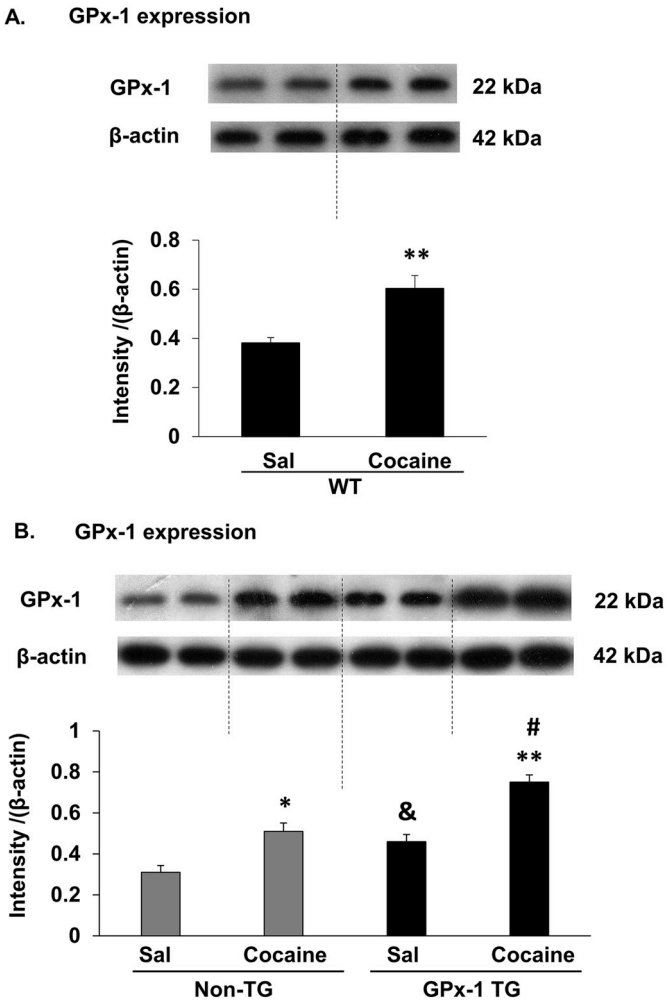

Fig. 2. Cocaine-induced changes in GPx-1 expression in the striatum of wild type (WT), non-transgenic (non-TG) and GPx-1 overexpressing transgenic (GPx-1 TG) mice. Sal = Saline. Each value is the mean ± S.E.M of six animals. *p < 0.05, **p < 0.01 vs. corresponding saline. #p < 0.01 vs. cocaine/non-TG mice. &p < 0.05 vs. corresponding non-TG saline [*t*-test (A) or two-way ANOVA (B). Post-hoc Fisher's LSD pairwise comparisons were followed (B)].

2.12. Statistical analysis

ANOVA followed by Fisher's LSD pairwise comparisons were applied to analyze the data. P-values of less than 0.05 were considered statistically significant.

3. Results

3.1. Cocaine-induced increases in GPx-1 expression in the striatum of mice

According to Fig. 1 of the experimental design, we sacrificed mice to investigate the changes in GPx-1 expression in the striatum of the wild type (WT) mice. GPx-1 expression was significantly increased in the striatum ($p = 0.002$ vs. saline) of WT mice after cocaine treatment [$t(10) = -4.148$, $p = 0.002$ (Fig. 2A)]. Cocaine treatment significantly increased GPx-1 expression in the striatum ($p = 0.021$ vs. saline) of non-TG mice [$F(3, 20) = 10.308$, $p = 2.5 \times 10^{-5}$ (Fig. 2B)] > . The basal level of GPx-1 expression was significantly higher in GPx-1 TG ($p = 0.035$) than in non-TG mice. Cocaine-induced increases in GPx-1 expression were more pronounced in GPx-1 TG > ($p = 0.007$) than in non-TG mice.

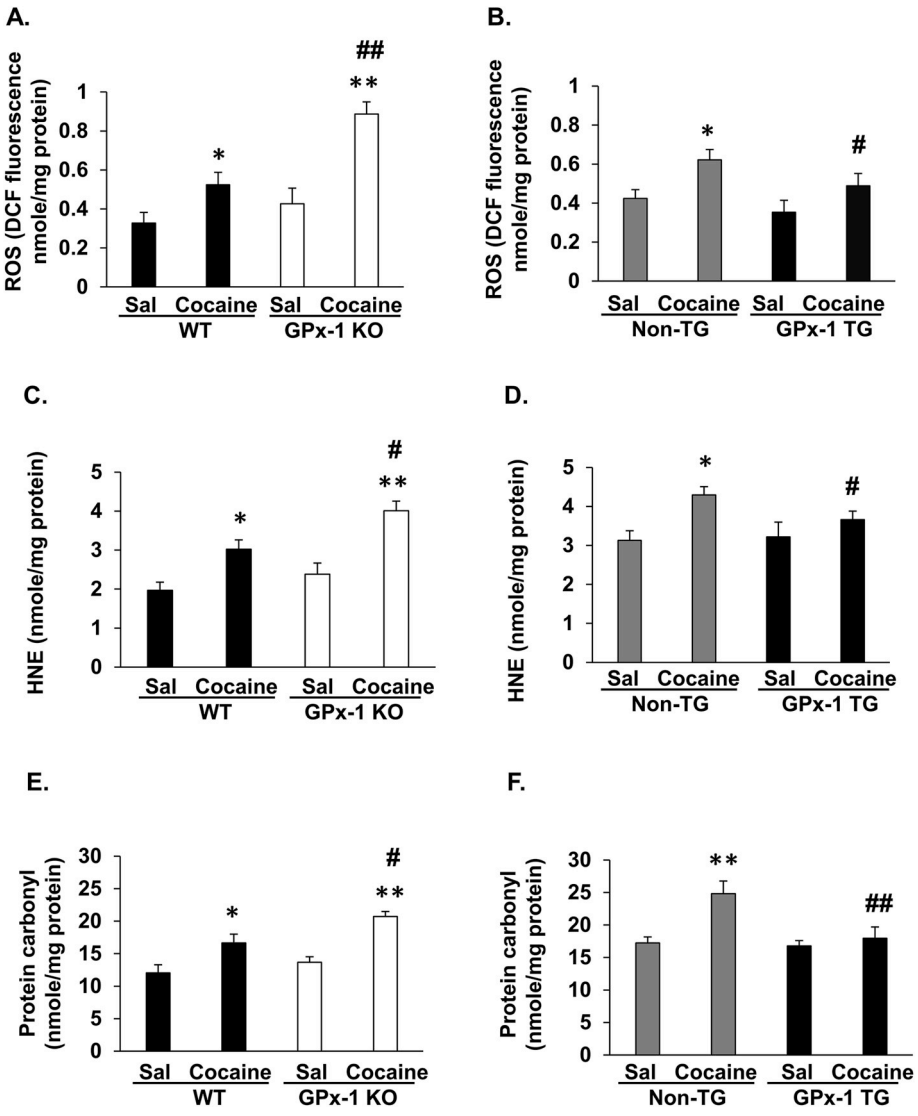

Fig. 3. Cocaine-induced changes in reactive oxygen species (ROS)(A, B), 4-hydroxy-2-nonenal (HNE) (C, D), and protein carbonyl (E, F) levels in the striatum of wild type (WT), GPx-1 knockout (GPx-1 KO), non-transgenic (non-TG) and GPx-1 overexpressing transgenic (GPx-1 TG) mice. Sal = Saline. Each value is the mean ± S.E.M of six animals. *p < 0.05, **p < 0.01 vs. corresponding saline, $^{\#}$p < 0.05, $^{\#\#}$p < 0.01 vs. cocaine/WT or cocaine/non-TG (two-way ANOVA followed by Fisher's LSD pairwise comparisons).

3.2. Cocaine-induced change in oxidative parameters in the striatum of wild type (WT), GPx-1 knockout (GPx-1KO), non-transgenic (non-TG) and GPx-1 overexpressing transgenic (GPx-1 TG) mice

As shown in Fig. 3, we examined the levels of reactive oxygen species (ROS), 4-hydroxynonenal (HNE), and protein carbonyl after cocaine treatment in the striatum of WT, GPx-1 KO, non-TG, and GPx-1 TG mice. Cocaine-treated WT mice showed a significant increase in ROS formation ($p = 0.045$ vs. corresponding saline). This increase was more pronounced in cocaine-treated GPx-1 KO mice ($p = 3.4 \times 10^{-5}$ vs. corresponding saline; $p = 0.001$ vs. cocaine-treated WT mice) [$F(3, 20) = 14.186$, $p = 3.4 \times 10^{-5}$ (Fig. 3A)]. In contrast, cocaine-treated non-TG also showed a significant increase in ROS formation ($p = 0.013$ vs. corresponding saline). Genetic overexpression of GPx-1 significantly attenuated ($p = 0.037$) ROS formation of cocaine-treated non-TG mice [$F(3, 20) = 4.899$, $p = 0.01$ (Fig. 3B)]. This phenomenon, in the case of ROS, was consistently comparable to that of HNE or protein carbonyl (Fig. 3C–F).

3.3. Cocaine-induced change in NFκB activity in the striatum of wild type (WT), GPx-1 knockout (GPx-1KO), non-transgenic (non-TG) and GPx-1 overexpressing transgenic (GPx-1 TG) mice

As shown in Fig. 4, we examined the cytosolic and nuclear expression levels of NFκB and its DNA binding activity in the striatum of WT, GPx-1 KO, non-TG, and GPx-1 TG mice. Cocaine treatment significantly decreased cytosolic NFκB expression in WT ($p = 0.016$). This decrease was more pronounced ($p = 9.7 \times 10^{-6}$) in cocaine-treated GPx-1 KO than in cocaine-treated WT mice [$F(3, 20) = 15.281$, $p = 2.1 \times 10^{-5}$ (Fig. 4A)]. In addition, cocaine-treatment significantly decreased cytosolic NFκB expression ($p = 5.4 \times 10^{-5}$ vs. saline) in non-TG. Cytosolic NFκB expression was higher ($p = 0.001$) in cocaine-treated GPx-1 TG than in cocaine-treated non-TG mice [$F(3, 20) = 11.075$, $p = 1.68 \times 10^{-4}$ (Fig. 4B)].

In contrast, cocaine treatment significantly increased NFκB nuclear translocation [$F(3, 20) = 47.367$, $p = 2.84 \times 10^{-9}$ (Fig. 4C)] and DNA binding activity [$F(3, 20) = 22.209$, $p = 1.41 \times 10^{-6}$ (Fig. 4E)] in the striatum of GPx-1 KO (both nuclear translocation and DNA binding activity; $p = 1.4 \times 10^{-2}$ and $p = 0.01$ vs. saline/GPx-1 KO) and this increment in GPx-1 KO mice was higher ($p = 1.5 \times 10^{-5}$ and

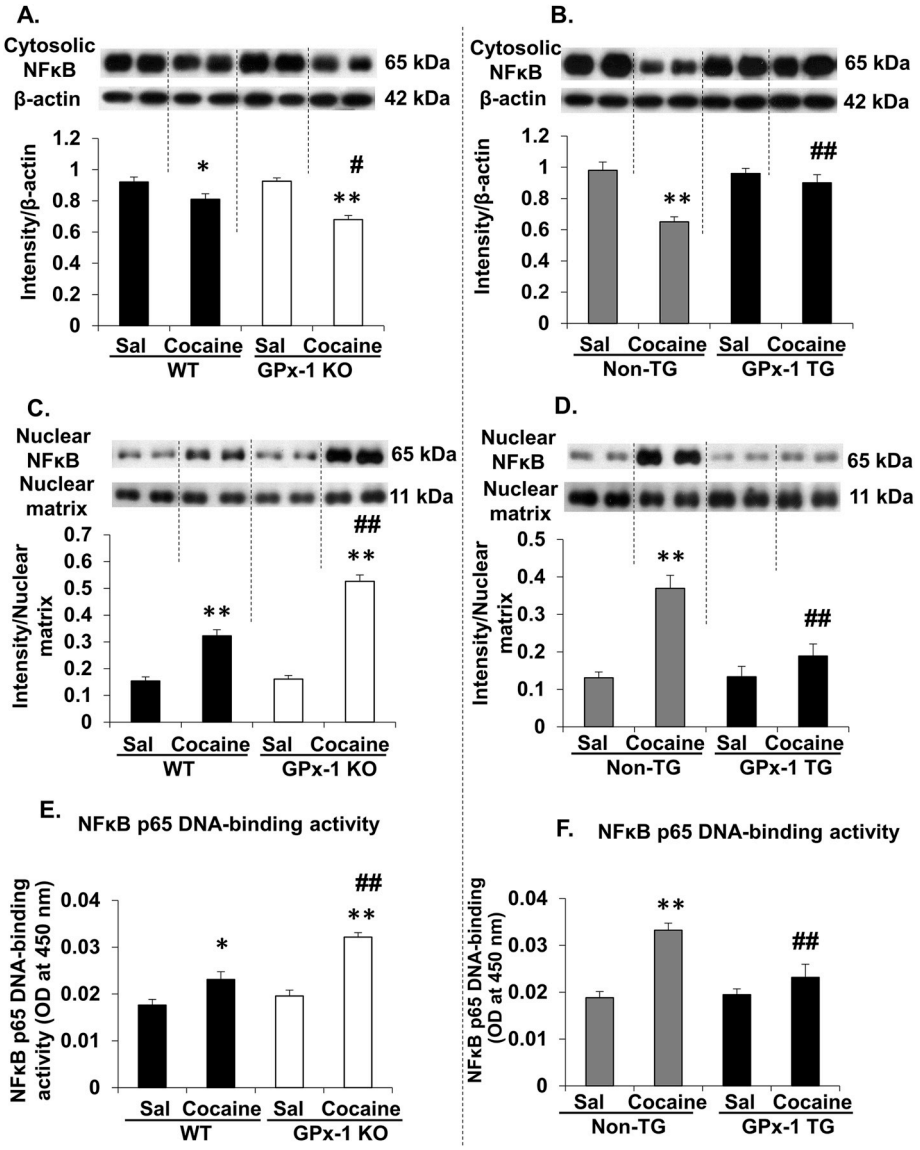

Fig. 4. Cocaine-induced changes in cytosolic (A, B) and nuclear NFκB expression (C, D), and NFκB DNA binding activity (E, F) in the striatum of wild type (WT), GPx-1 knockout (GPx-1 KO), non-transgenic (non-TG) and GPx-1 overexpressing transgenic (GPx-1 TG) mice. Sal = Saline. Each value is the mean ± S.E.M of six animals. *$p < 0.05$, **$p < 0.01$ vs. corresponding saline, $^{\#}p < 0.05$, $^{\#\#}p < 0.01$ vs. cocaine/WT or cocaine/non-TG (two-way ANOVA followed by Fisher's LSD pairwise comparisons).

$p = 1.44 \times 10^{-4}$ vs. cocaine/WT) than in WT mice. In contrast, cocaine-induced increases in NFκB nuclear translocation [$F(3, 20) = 14.837$, $p = 2.57 \times 10^{-5}$ (Fig. 4D)] and DNA binding activity [$F(3, 20) = 12.672$, $p = 7.266 \times 10^{-5}$ (Fig. 4F)] were more evident in non-TG ($p = 2.97 \times 10^{-4}$ and $p = 0.001$ vs. cocaine/GPx-1 TG) than in GPx-1 TG, indicating that genetic overexpression of GPx-1 significantly attenuated NFκB nuclear translocation and DNA binding activity induced by cocaine.

3.4. Effects of pyrrolidine dithiocarbamate (PDTC, a NFκB inhibitor) on cocaine-induced increases in c-Fos-immunoreactivity (c-Fos-IR) in the nucleus accumbens (NAc) of wild type (WT), GPx-1 knockout (GPx-1 KO), non-transgenic (non-TG) and GPx-1 overexpressing transgenic (GPx-1 TG) mice

We then examined c-Fos-IR to investigate cocaine-induced neural stimulation in the NAc of GPx-1 KO and GPx-1 TG mice (Fig. 5). A very little c-Fos-IR was observed in the absence of cocaine, and c-Fos-IR was significantly increased ($p = 1.15 \times 10^{-5}$ vs. corresponding saline) after the final cocaine treatment in WT mice [$F(7, 40) = 49.967$, $p = 8.6 \times 10^{-18}$ (Fig. 5A)]. Cocaine-induced increments in c-Fos-IR were more pronounced in GPx-1 KO ($p = 8.12 \times 10^{-11}$ vs. cocaine/WT) than in WT mice. These increases were significantly reversed by PDTC, a NFκB inhibitor in WT mice ($p = 0.038$ vs. cocaine/WT) and GPx-1 KO mice ($p = 6.12 \times 10^{-7}$ vs. cocaine/GPx-1 KO). In addition, a cocaine-induced significant increase ($p = 6.19 \times 10^{-10}$) in c-Fos-IR was observed in non-TG mice. PDTC treatment significantly attenuated ($p = 0.006$) this increase in non-TG mice. Genetic overexpression of GPx-1 significantly attenuated ($p = 10^{-5}$ vs. cocaine/non-TG) cocaine-induced c-Fos-IR. However, PDTC treatment did not show any additive effects on the attenuation by genetic overexpression of GPx-1 [$F(7, 40) = 17.296$, $p = 2.68 \times 10^{-10}$ (Fig. 5B)].

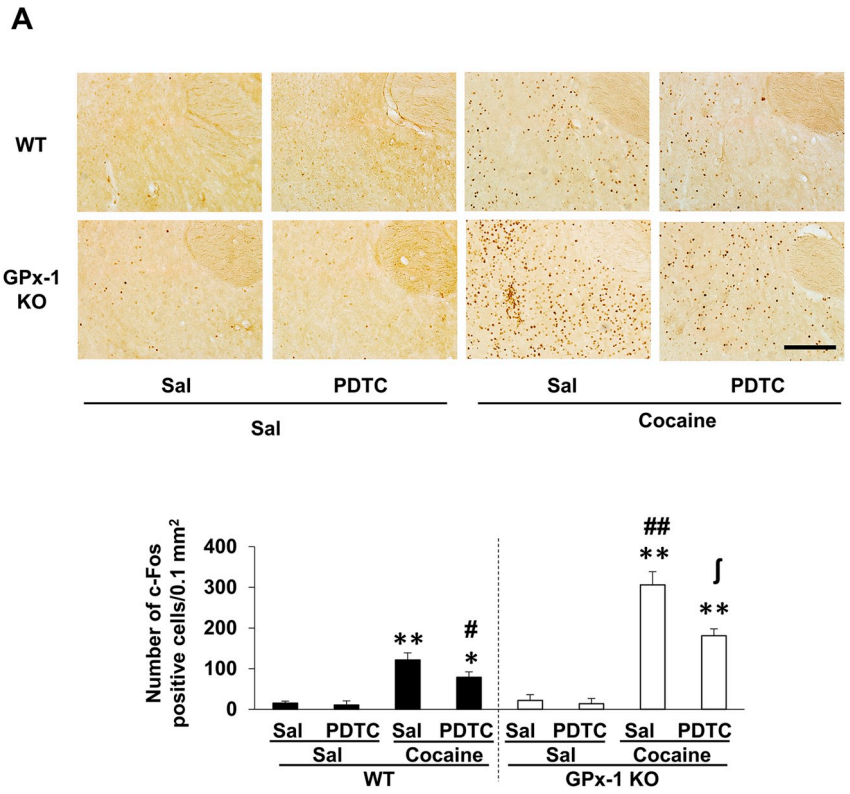

Fig. 5. Effects of pyrrolidine dithiocarbamate (PDTC, a NFκB inhibitor) on cocaine-induced c-Fos-IR in the nucleus accumbens of wild type (WT), GPx-1 knockout (GPx-1 KO), non-transgenic (non-TG) and GPx-1 overexpressing transgenic (GPx-1 TG) mice. Each value is the mean ± SEM of six mice. *$p < 0.05$, **$p < 0.01$ vs. corresponding saline. $^{\#}p < 0.05$, $^{\#\#}p < 0.01$ vs. cocaine/WT or cocaine/non-TG. $^{\int}p < 0.01$ vs. cocaine/GPx-1 KO (three-way ANOVA followed by Fisher's LSD pair-wise comparisons). Scale bar = 200 μm.

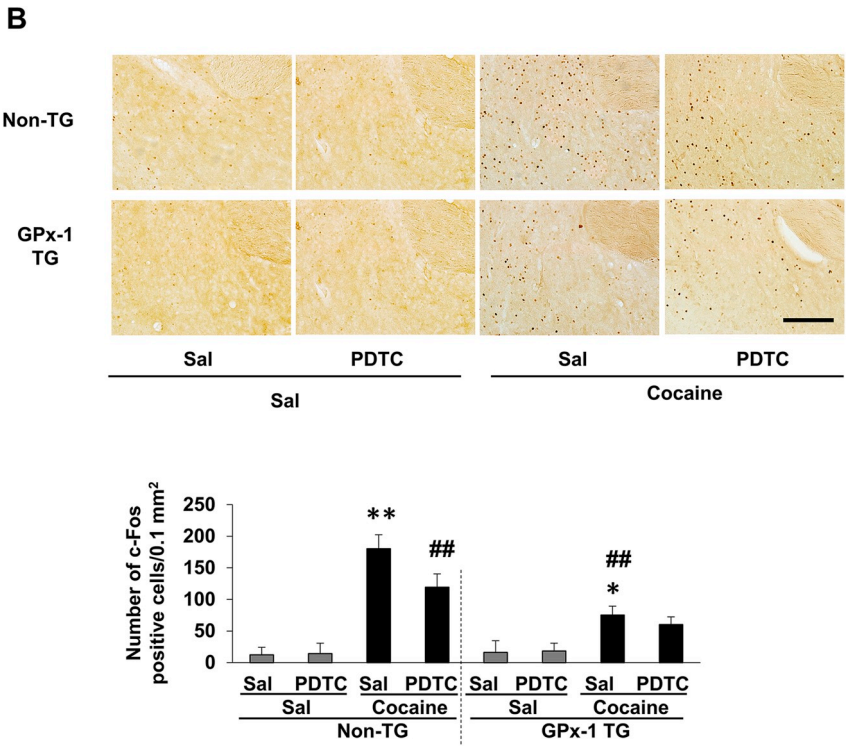

Fig. 5. (*continued*)

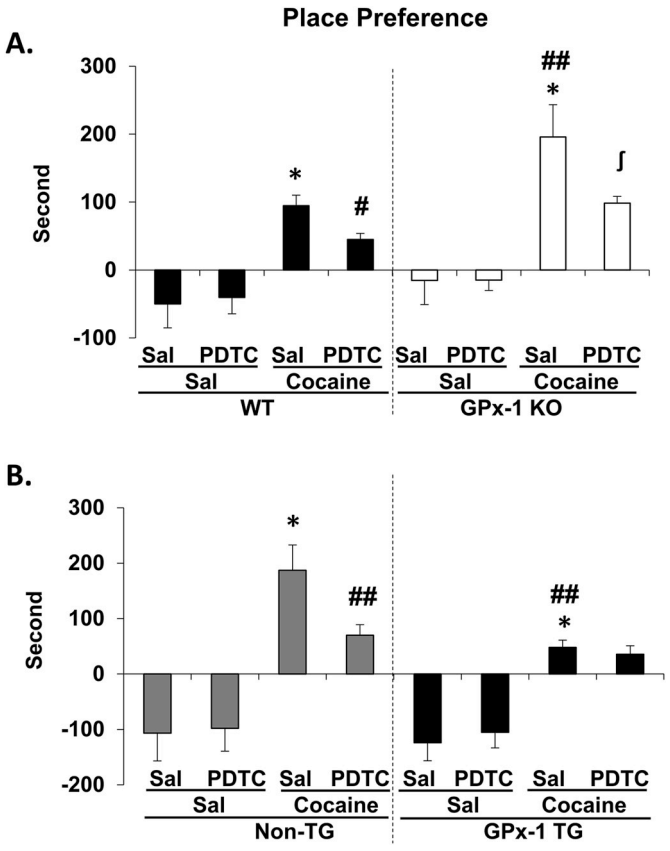

Fig. 6. Effects of pyrrolidine dithiocarbamate (PDTC, a NFκB inhibitor) on cocaine-induced conditioned place preference (CPP) in wild type (WT), GPx-1 knockout (GPx-1 KO) (A), non-transgenic (non-TG) and GPx-1 overexpressing transgenic (GPx-1 TG) (B) mice. Each value is the mean ± SEM of ten mice. *$p < 0.01$ vs. corresponding saline. $^{\#}p < 0.05$, $^{\#\#}p < 0.01$ vs. cocaine/WT or cocaine/non-TG. $^{\int}p < 0.01$ vs. cocaine/GPx-1 KO (three-way ANOVA followed by Fisher's LSD pair-wise comparisons).

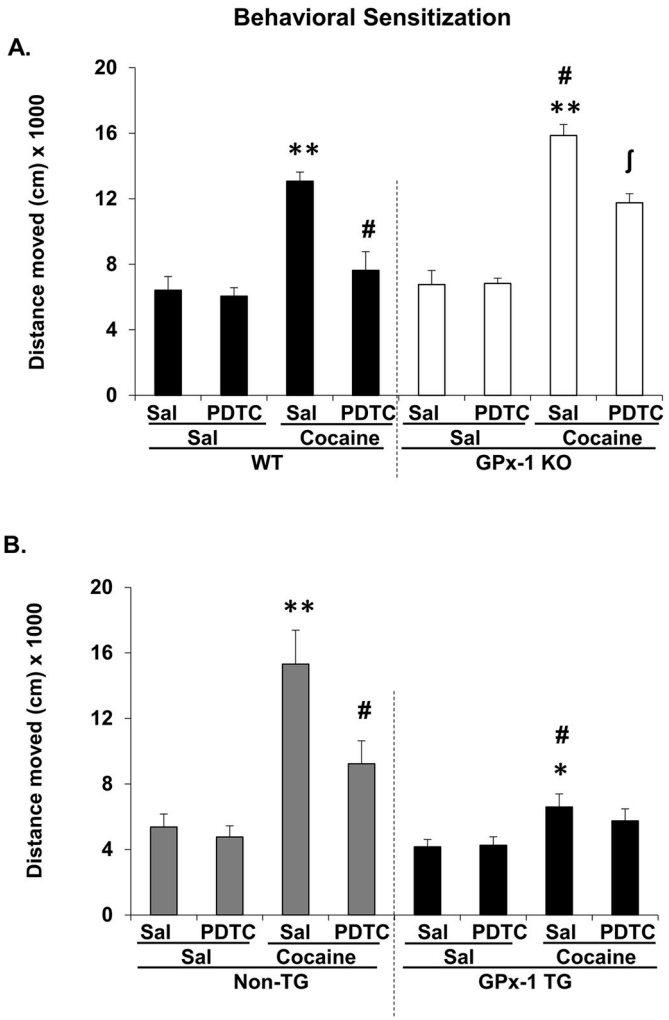

Fig. 7. Effects of pyrrolidine dithiocarbamate (PDTC, a NFκB inhibitor) on cocaine-induced behavioral sensitization in wild type (WT), GPx-1 knockout (GPx-1 KO) (A), non-transgenic (non-TG) and GPx-1 overexpressing transgenic (GPx-1 TG) (B) mice. Each value is the mean ± SEM of ten mice. *$p < 0.05$, **$p < 0.01$ vs. corresponding saline. $^{\#}p < 0.01$ vs. cocaine/WT or cocaine/non-TG. $^{\int}p < 0.01$ vs. cocaine/GPx-1 KO (three-way ANOVA followed by Fisher's LSD pair-wise comparisons).

3.5. Effects of PDTC, a NFκB inhibitor, on cocaine-induced conditioned place preference (CPP) and behavioral sensitization in of wild type (WT), GPx-1 knockout (GPx-1KO), non-transgenic (non-TG) and GPx-1 overexpressing transgenic (GPx-1 TG) mice

CPP and behavioral sensitization induced by cocaine were shown in Figs. 6 and 7. In the absence of cocaine, CPP was not induced in the mice. Cocaine-induced CPP ($p = 9.21 \times 10^{-6}$ vs. Saline-treated WT) was observed in WT mice. This CPP was more evident in GPx-1 KO ($p = 0.006$) than in WT. In addition, cocaine-induced CPP ($p = 6.96 \times 10^{-10}$ vs. Saline-treated non-TG) was also significantly increased in non-TG mice. However, this increase was significantly inhibited by genetic overexpression of GPx-1 ($p = 0.001$ vs. cocaine-treated non-TG). PDTC treatment significantly attenuated cocaine-induced CPP (WT: $p = 0.049$ vs. Saline/cocaine; GPx-1 KO: $p = 0.001$ vs. Saline/cocaine; Non-TG: $p = 0.006$ vs. Saline/cocaine). However, PDTC did not show any additive effect against attenuation offered by genetic overexpression of GPx-1, indicating that NFκB is a critical mediator for the protective potential of GPx-1.

The changes in locomotor activity over time are presented in Supplementary Fig. S1. Notably, although the first challenge of cocaine significantly increased locomotor activity in WT, GPx-1 KO, non-TG and GPx-1 TG mice, PDTC did not affect the hyperlocomotion induced by cocaine (Supplementary Fig. S2). The profile of behavioral sensitization is comparable to that of CPP. Cocaine-induced behavioral sensitization was significantly observed in WT ($p = 3.03 \times 10^{-10}$ vs. saline-treated WT mice). The behavioral sensitization is more pronounced in GPx-1 KO mice ($p = 0.003$ vs. cocaine-treated WT mice). Genetic overexpression of GPx-1 significantly attenuated the behavioral sensitization ($p = 6.44 \times 10^{-8}$ vs. cocaine-treated non-TG mice). Similar to CPP, PDTC treatment significantly attenuated cocaine-induced behavioral sensitization (WT: $p = 8.07 \times 10^{-8}$ vs. Saline/cocaine; GPx-1 KO: $p = 2.5 \times 10^{-5}$ vs. Saline/cocaine; Non-TG: $p = 7.5 \times 10^{-5}$ vs. Saline/cocaine). However, PDTC did not show any additional effects against protective activity mediated by genetic overexpression of GPx-1.

4. Discussion

Cocaine treatment was found to significantly induce GPx-1 expression, oxidative parameters, NFκB activity, c-Fos-IR in the striatal complex of mice. Importantly, oxidative parameters, NFκB activity, and c-Fos-IR were more pronounced in GPx-1 KO than in WT mice, and were attenuated by PDTC, a NFκB inhibitor. In addition, PDTC did not demonstrated any additional positive effects against the protective potentials mediated by the genetic overexpression of GPx-1, suggesting that NFκB is a critical mediator of the protective potential of GPx-1 in cocaine-induced CPP and behavioral sensitization. Here, we suggest

that cocaine treatment facilitates NFκB nuclear translocation and DNA binding activity in striatal tissues in response to oxidative stress, and that cocaine-induced oxidative stress activates NFκB induction, which could possibly be attenuated by the compensative induction of GPx-1.

In our study, repeated cocaine treatment resulted in a significant increase in superoxide dismutase (SOD) activity in the striatum of wild type mice, but did not involve in a concomitant increase in GPx activity (Supplementary Fig. S3). Increased SOD activity may lead to an accumulation of H_2O_2, which in the absence of simultaneous increases in the activity of GPx, could induce a Fenton reaction, leading to the formation of lipid peroxidation/protein oxidation, resulting in irreversible cellular damage (Shin et al., 2014). Our observation of increased ROS/lipid peroxidation/protein oxidation products implies that GPx activity, rather than increased SOD, modulates these endpoints. However, the underlying mechanism of cocaine-induced decrease in glutathione-S-transferase (Supplementary Figs. S3E–F) remains to be elucidated.

It is well-known that dopamine plays a crucial role in cocaine-induced CPP and behavioral sensitization. The significant increase of dopamine release due to the binding of cocaine to the transporter sites of monoamines results in the inhibition of their uptake in the presynaptic neuron (Foley, 2005; Vitcheva et al., 2015). Therefore, we speculate that cocaine-induced increase in extracellular dopamine will be more pronounced in GPx-1 KO than in WT mice. In addition, this increase in extracellular dopamine might be attenuated by GPx-1 overexpression or PDTC, although evidence for this is lacking. Similarly, we cannot rule out the possibility that cocaine-induced increase in c-Fos-immunoreactivity in the NAc of GPx-1 KO (Fig. 5A) might be comparable to increase in extracellular dopamine levels, and this phenomenon may be less pronounced in GPx-1 overexpression (Fig. 5B) or PDTC treatment in mice than GPx-1 depletion in mice.

Lubos et al. (2011) indicated that GPx-1 overexpression *itself* has been shown to initially and significantly suppress the activation of NFκB pathway. Therefore, cocaine-induced CPP and behavioral sensitization cannot be further attenuated by PDTC in GPx-1 TG mice (Figs. 6–7). Similarly, we have demonstrated this phenomenon in our previous reports (Shin et al., 2018; Tran et al., 2017).

Most previous studies have emphasized the putative role of oxidative stress as a crucial mediator for cocaine-induced neuronal cell death in brain reward systems (Kovacic, 2005). In line with current result, previous studies suggest that oxidative stress in the brain reward system is associated with cocaine psychomotor responses (Numa et al., 2008; Uys et al., 2011). Previous investigations have demonstrated that the superoxide scavenger 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPOL) can attenuate oxidative stress in the prefrontal cortex (PFC) and NAc as well as the development of behavioral sensitization induced by cocaine (Numa et al., 2008).

Consistently, TEMPOL is also involved in regulating cocaine reward as measured by the CPP model in rats. Substantial behavioral changes in the TEMPOL-administered animals correlated with attenuation of cocaine-induced oxidative damage in their NAc and PFC (Beiser et al., 2017).

Jang et al. (2015) demonstrated that ROS produced by cocaine exposure is localized in the nucleus accumbal neurons. In addition, they observed that intra-NAc infusion of TEMPOL decreases ROS formation in the accumbal neurons, and cocaine self-administration in rats, suggesting that cocaine drug intoxication is associated with generation of superoxide in neurons of the NAc. Because the basal activity of SOD in NAc was lowest in the brain of rats (Carvalho et al., 2001), it is plausible that nucleus accumbal oxidative burdens mediate cocaine drug dependence. In addition, it is recognized that alteration of enzymatic oxidants may result in accumulations of hydrogen peroxide/peroxide (Shin et al., 2017). Recently, we demonstrated, for the first time, that hydrogen peroxide scavenger GPx-1 plays a protective role in memory impairments and behavioral sensitization induced by MA (Mai et al., 2018c, 2018d; Shin et al., 2017; Tran et al., 2018b). Our reports support current finding that GPx-1 gene attenuates cocaine-induced CPP and behavioral sensitization via antioxidant potential by modulation of NFκB in mice.

NFκB binding sites were identified in the promotor regions of genes encoding for oxidative/inflammatory cytokines (i.e., IL-1, IL-6, and TNFα). It is interesting that the expression of these cytokines is dependent on activated NFκB and, in turn, these cytokines can stimulate this transcription factor (Lee et al., 2001). Thus, it may be possible that cocaine-mediated cellular effects use NFκB to amplify their own signals.

It has also been shown that the activation of NFκB can enhance the ability of NFκB to bind DNA and induce gene transcription (Natoli et al., 2005; Wan and Lenardo, 2009). ROS are critical intermediates for various NFκB-activating signals (Schreck et al., 1992). Since it has been shown that the neurotoxic effects of drugs of abuse are often associated with oxidative stress among other mechanisms (Herrera et al., 2003; Numa et al., 2008), NFκB could be involved in drug-induced neuronal dysfunction and neurotoxicity.

Cocaine can decrease glutathione-dependent system and enhance NFκB and activator protein-1 (AP-1) binding activities as well as stimulate gene expression regulated by these transcription factors. The AP-1 protein c-Fos encodes nuclear transcription of genes involved in the transmission of inter- and intracellular information through multiple signaling transduction pathways. c-Fos may function in coupled short-term changes in cellular phenotype by modulating the expression of specific target genes. It is well-established that dopamine receptor stimulation or psychostimulation (i.e., MA and cocaine) increases c-Fos expression, eventually resulting in oxidative damage and abnormal behavior. We observed that behavioral responses induced by MA (Mai et al., 2018c; Shin et al., 2009) are comparable to those induced by cocaine (current finding). NAc belongs to striatal complex and NAc is recognized as the most sensitive region in response to the neuronal stimulation. For example, c-Fos-IR was more pronounced in NAc than in other striatal areas (Gerth et al., 2017; Mai et al., 2018c; Shin et al., 2004b > ; Vassoler et al., 2013). Consistently, behavioral responses induced by MA or cocaine paralleled those of c-Fos-IR in NAc. Enhanced c-Fos-IR prevented by the overexpression of GPx-1 gene, reflecting that the protective potential of GPx-1 (antiperoxidative system) in CPP and behavioral sensitization induced by cocaine.

The nucleus accumbens (NAc) is a part of the mesolimbic reward circuit, and is a major target of drugs of abuse, including opiates and psychostimulants (Boileau et al., 2003; Salgado and Kaplitt, 2015). Previous exposure to cocaine increases preference for the drug and increases self-administration of the drug (Ahmed and Koob, 1998; Ahmed et al., 2003; Ferrario et al., 2005; Renthal et al., 2007; Shippenberg and Heidbreder, 1995). Drug regimens that increase the frequency of motivated behaviors also cause long-lasting structural changes within the NAc. Chronic cocaine treatment increased the NFκB activity in the striatal complex (including NAc), while inhibition of NFκB activity blocked the cocaine-induced behavioral response. Here, we observed that NFκB inhibition significantly ameliorates CPP and behavioral sensitization induced by cocaine in GPx-1 KO mice. However, NFκB inhibition did not show any additive effects in response to protective potentials conveyed by genetic overexpression of GPx-1, suggesting that NFκB is a neuropsychoprotective target for GPx-1 gene in response to cocaine drug dependence.

GPx mRNA was found in all regions of basal ganglia (Kunikowska and Jenner, 2002). This wide distribution of GPx mRNA throughout rat basal ganglia correlates well with that of its protein in both human (Damier et al., 1993) and murine brain tissue (Trepanier et al., 1996), and enzyme activity in rodent brain tissue (Brannan et al., 1980). GPx has been found in glial cells, in particular astrocytes (Pearce et al., 1997). The striatal area appeared to express higher levels of GPx mRNA than other basal ganglial areas (Kunikowska and Jenner, 2002), suggesting that the striatal area may be relatively vulnerable to oxidative damage, and thus dependent upon the high antioxidant capacity provided by GPx. Importantly, disruption in astrocyte-mediated modulation of neural function has been implicated in the abusive process

(Verkhratsky and Parpura, 2016). In addition, Scofield et al. (2016) provide a novel evidence of astrocyte dysfunction within the NAc of cocaine-experienced animals. Therefore, role of GPx-1 in cocaine-caused astrocytic alteration in NAc remains to be further elucidated.

In summary, in this study, we demonstrate that the GPx-1 gene protects against CPP and behavioral sensitization induced by cocaine by inhibiting oxidative burdens via modulation of NFκB signaling. Finally, we propose that the GPx-1 gene offers a potential therapeutic target against drug dependence induced by cocaine, although precise mechanism remains to be further characterized.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuint.2019.01.018.

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