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MPTP neurotoxicity is highly concordant between the sexes among BXD recombinant inbred mouse strains

Gelareh Alam[a], Diane B. Miller[b], James P. O'Callaghan[b], Lu Lu[c,d], Robert W. Williams[c], Byron C. Jones[a,c,*]

[a] Department of Pharmaceutical Sciences, Northeast Ohio Medical School, Rootstown, OH, United States
[b] Centers for Disease Control and Prevention–National Institute for Occupational Safety and Health, Morgantown, WV, United States
[c] University of Tennessee Health Science Center, Memphis, TN, United States
[d] Jiangsu Key Laboratory of Neuroregeneration, Nantong University, Nantong 226001, People's Republic of China

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ABSTRACT

Continuing our previous work in which we showed wide-ranging strain differences in MPTP neurotoxicity in male mice among ten BXD recombinant inbred strains, we replicated our work in females from nine of the same strains. Mice received a single s.c. injection of 12.5 mg/kg MPTP or saline. Forty-eight hours later the striatum was dissected for neurochemical analysis. Striatal dopamine (DA) and its metabolites, DOPAC and HVA, striatal serotonin (5-HT) and its metabolite, 5-HIAA, were analyzed using HPLC. Tyrosine hydroxylase (TH) and glial fibrillary acidic protein (GFAP), an astrocytic protein that increases during the astroglial response to neural injury, were measured using ELISA. There were wide genetic variations in the DA, DOPAC, HVA, TH and GFAP responses to MPTP. We also performed principal component analysis (PCA) on the difference values, saline minus MPTP, for DA, DOPAC, HVA and TH and mapped the dominant principal component to a suggestive QTL on chromosome 1 at the same location that we observed previously for males. Moreover, there were significant correlations between the sexes for the effect of MPTP on DA, HVA, and TH. Our findings suggest that the systems genetic approach as utilized here can help researchers understand the role of sex in individual differences. The same approach can pave the way to understand and pinpoint the genetic bases for individual differences in pathology attributable to toxicants. Such systems genetics approach has broad implications for elucidating gene-environment contributions to neurodegenerative diseases.

1. Introduction

Heavy metals, multiple pesticides and herbicides are considered to be risk factors for human health as acute and chronic exposure to them is linked to an increased risk for development of neurodegenerative diseases such as Parkinson's disease (PD) (Hertzman et al., 1990; Liou et al., 1997; Landrigan et al., 2005; McCormack et al., 2005; Tanner et al., 2011). The picture concerning exposure to pesticides and neurodegenerative diseases however is not clear as there are several conflicting reports regarding these agents as increasing risk for sporadic Parkinson's disease (sPD, Elbaz et al., 2009; Gatto et al., 2009; Firestone et al., 2010). Differential vulnerability to complex neurological disorders, including PD is acknowledged to be related at least in part to host susceptibility (i.e., susceptible genotypes exposed to environmental risk factors).

There are a number of approaches to assess how the host responds to a toxic insult. One involves epidemiological studies in which subpopulations carrying potential susceptible genotypes are recruited and examined for response to the toxicant. Identifying such individuals is challenging, but possible (Goldman et al., 2012). Another is the use of genetically defined animal models that mimic the individual differences observed in humans (Taylor et al., 1973). There are several genetic reference populations of animals, especially mice. One such genetic reference population or model is recombinant inbred (RI) strains. RI mice are derived from two parental inbred strains by first making an F_1 generation of the parents, and from the F_1 population, making F_2 and more advanced intercrosses, making families and inbreeding by brother-

* Corresponding author at: Department of Genetics, Genomics, and Informatics, University of Tennessee Health Science Center, 71 S. Manassas Street, Memphis, TN 38163, United States.
E-mail address: bjone129@UTHSC.edu (B.C. Jones).

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sister matings for 20 generations or more. In this particular model the allelic differences between two or more parental lines segregate among a large population of independently derived, but related lines of progeny (Peirce et al., 2004). This approach enables researchers to relate genomic polymorphisms to phenotypic variations in normal or pathological states and therefore assess the genetic basis for individual differences in phenotypes. Furthermore, using this approach we can assess the genetic basis for individual differences and more importantly, gene-environment and gene-gene interactions underlying these differences. Thus RI strains of rodents constitute an invaluable research tool to aid in identifying the underlying causes of major diseases, including neurodegenerative diseases. We recently reported large strain differences in the dopaminergic neurotoxicity of 1-methyl-4-phenyl-1,2,3,6-tetrahydro-pyridine (MPTP) in male BXD RI mice derived from C57BL/6J and DBA/2J parental strains (Jones et al., 2013). MPTP is a prototypical pro-neurotoxicant that targets dopaminergic cells of the nigrostriatal pathway of the brain and is broadly used in animals to investigate the factors contributing to the vulnerability of the nigro-striatal pathway to toxic insult (O'Callaghan et al., 1990).

Others have addressed genetic-based difference in susceptibility to MPTP neurotoxicity by evaluating the effects of this agent in different strains of mice, usually males, and have nominated candidate genes on chromosomes 1 (Cook et al., 2003), 13 and 15 (Sedelis et al., 2003). The use of male animals to investigate host susceptibility to MPTP and other neurotoxicants, may be too narrowly focused as we see sex differences in many neurological disorders. For example the prevalence of PD, a disorder characterized by degeneration of the nigro-striatal pathway, is higher in men compared to women. There are experimental studies showing the protective effect of estrogen on the nigrostriatal pathway and dopaminergic cells concerning the neurotoxicity of MPTP and methamphetamine in C57BL/6J mice (Dluzen et al., 1996; Miller et al., 1998). Such findings suggest that in order to more fully elucidate the role of host susceptibility, both sexes should be evaluated. Accordingly, the main purpose of this study was to expand on our previous work in which we reported differences in genetic-based susceptibility to MPTP in male BXD RI mice (Jones et al., 2013). Here, we report strain differences in MPTP neurotoxicity in females and the sexes combined to show where they agree and where they appear to differ regarding MPTP neurotoxicity. Our data show a remarkable concordance between the female and male BXD mice for DA-based MPTP toxicity in the striatum.

2. Materials and methods

2.1. Animals

Female mice (age range from 2 to 8 months) from nine of the ten BXD strains utilized to evaluate MPTP neurotoxicity that we reported results in males (Jones et al., 2013) were used. One strain, BXD27 is a poor breeder and no female mice were available. Ten days prior to MPTP treatment, all of the animals were transferred from the University of Tennessee Health Science Center to the Centers for Disease Control, National Institute of Occupational Safety and Health (NIOSH) laboratory in Morgantown, West Virginia. The animals were maintained on a 12:12 h light and dark cycle and had free access to food and water. All procedures conducted on the animals were approved by the NIOSH Institutional Animal Care and use Committee and in accordance with the NRC guide for the Care and Use of Laboratory Animals (National Academy Press, 1996). NIOSH is an AAALAC accredited institution.

2.2. MPTP and reagents

MPTP-HCl used in the study was provided by Aldrich (Milwaukee, WI, USA). Mouse anti-rat tyrosine hydroxylase (TH) monoclonal antibody and rabbit anti-rat TH polyclonal antibody were purchased from Sigma (St. Louis, MO) and Calbiochem (San Diego, CA) respectively. Details regarding GFAP antibodies used in the study can be found in O'Callaghan (2002).

2.3. MPTP treatment and brain dissection

All mice were injected s.c. with 12.5 mg/kg MPTP or saline (O'Callaghan et al., 1990). We have previously shown this dosing regimen to have a significant effect on the striatum as evidenced by a decrease in DA and its metabolites, a loss in TH protein and an increase in GFAP indicating an astrogliosis in response to injury. Also the regimen produces minimal to no damage to DA cell bodies in the substantia nigra pars compacta (SNc). All of the animals were decapitated forty-eight hours after injection and the striatum dissected for neurochemical analysis.

2.4. Biochemical assays

Following the same procedures (see Jones et al., 2013) we measured striatal monoamines by HPLC with electrochemical detection from the left striatum and TH and GFAP by sandwich ELISA in the right side (O'Callaghan, 1991, 2002; Sriram et al., 2004; O'Callaghan et al., 2014). Values for the monoamines were normalized by tissue weight and the TH and GFAP values were normalized to total homogenate protein assayed by BCA (Smith et al., 1985).

2.5. Data analysis

Three between-subjects factors (strain, sex, treatment) analysis of variance (ANOVA) was used to evaluate the data (SAS Institute Cary NC). Pairwise comparisons were made using the Tukey HSD test with α set at 0.05. The male data used for comparisons here are from Jones et al. (2013). We also performed principal component analysis (PCA) on the difference values, saline minus MPTP, for DA, DOPAC, HVA and TH for quantitative trait loci (QTL) mapping of emergent eigentraits using the WebQTL software at www.genenetwork.org. Strain means for all data presented herein are available to anyone at no cost at this website.

3. Results

3.1. Effects of MPTP on DA neurochemistry in the striatum

3.1.1. Effects of MPTP on DA in the striatum

ANOVA revealed a significant main effect for strain with BXD32 and BXD48 having the lowest and highest DA concentrations respectively (Fig. 1, left panel). There were also significant main effects for treatment and sex. The strain × sex, treatment × strain and strain × sex × treatment interactions were also significant.

The percent of control (MPTP vs. saline) for DA in the striatum by sex is shown in Fig. 1, right panel. BXD40 showed the highest DA loss in the striatum in both sexes, BXD84 showed the least loss in females and BXD29 the least loss in males (Fig. 1, right panel).

3.1.2. Effects of MPTP on DOPAC in the striatum

Basal levels of DOPAC differed among the females with BXD40 and BXD69 showing the lowest and highest DOPAC levels respectively (Fig. 2, left panel). For sexes combined ANOVA revealed significant main effects of strain, sex and treatment. Significant strain × sex and strain × treatment interactions were

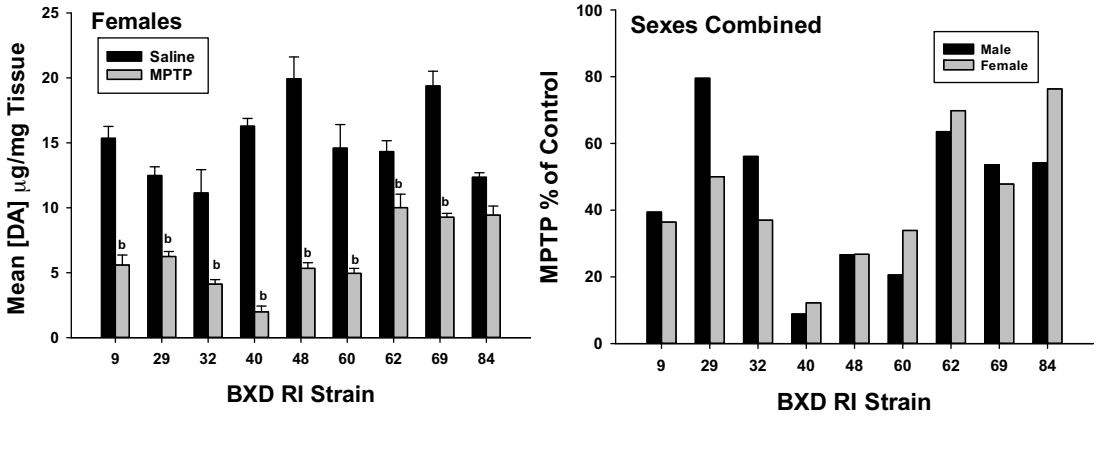

Fig. 1. Left panel. Effect of MPTP on DA concentration in the striatum in 9 strains of BXD recombinant inbred (RI) female mice. The mice were injected with12.5 mg/kg MPTP (vs. saline) and tissue collected 48 h later. DA content in the striatum was determined by HPLC, normalized to tissue wet weight and expressed as mean ± s.e.m. **Right panel.** Effect of MPTP in BXD mice expressed as% control, for both sexes. BXD40 showed the greatest MPTP-related DA loss for both sexes. ANOVA revealed a significant main effect for strain, sex and treatment ($F_{8,140} = 17.21$, $F_{1,140} = 7.77$, $F_{1,140} = 849.86$ respectively, $p < 0.01$ for each) and significant strain × sex, strain × treatment and strain × sex × treatment interaction ($F_{8,140} = 5.49$, $F_{8,140} = 17.37$ respectively, $p < 0.01$ for both, $F_{8,140} = 2.2$, $p < 0.05$ respectively). (n = 5 per strain and treatment, b $p < 0.05$, showing significant differences between saline and MPTP treated groups).

also observed. The percent of control (MPTP vs. saline) for DOPAC in the striatum by sex is shown in Fig. 1, right panel. BXD40 and BXD84 showed the highest and lowest DOPAC loss respectively in the striatum in both sexes.

3.1.3. Effects of MPTP on HVA in the striatum

ANOVA revealed significant main effects for strain and treatment. Significant differences in basal levels of HVA among females were observed with BXD9 and BXD32 having the highest and lowest HVA concentration respectively (Fig. 3 left panel). The main effect for sex was not significant. The strain × treatment interaction was significant. The Strain × sex, treatment × sex and strain × sex × treatment interactions were not significant. The percent of control (MPTP vs. saline) for HVA in the striatum in both sexes is shown in Fig. 3, right panel. Strain BXD40 has the highest HVA loss in both sexes.

3.1.4. Effects of MPTP on DA turnover, (DOPAC/DA)

ANOVA revealed significant main effects for strain with BXD48 and BXD69 62 having the lowest and highest basal levels of DOPAC/DA in females respectively (Fig. 4, left panel). ANOVA revealed significant effects for sex and treatment on DOPAC/DA. There were no significant differences in DOPAC/DA levels between saline and MPTP treated groups across the strains. DOPAC is one of two major metabolites, the other being homovanillic acid (HVA). DA turnover can thus be estimated by calculating the ratio of either metabolite to the amine. DOPAC/DA is considered to reflect presynaptic processes as DOPAC is produced by monoamine oxidase and HVA/DA is thought to reflect postsynaptic process as it is produced by catechol-O-methyltransferase. Changes in these indices can indicate pharmacological treatments, disease-relevant damage or compensation. Here, post hoc test revealed no differences between saline and MPTP groups across the strains. Strain × sex

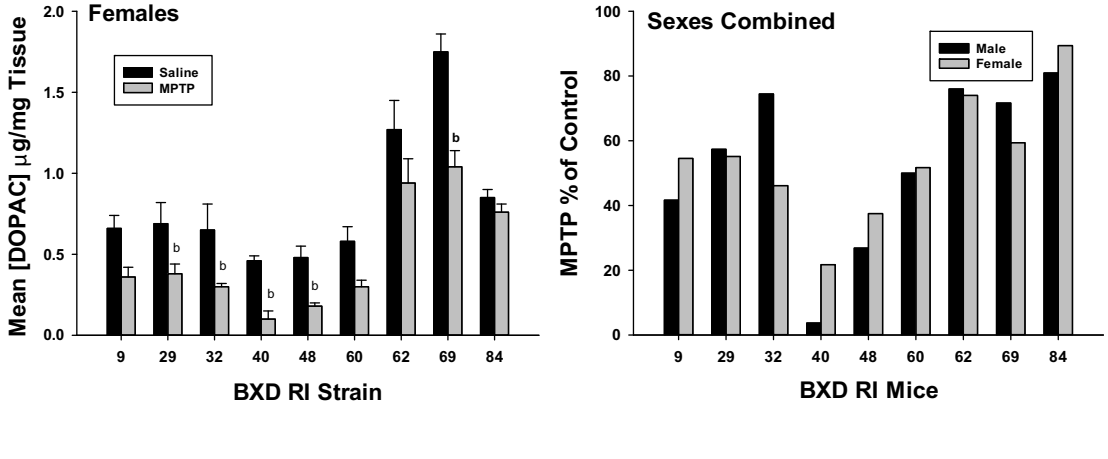

Fig. 2. Left panel. Effect of MPTP on striatal DOPAC in females. Mice were injected with 12.5 mg/kg MPTP (vs. saline) and tissue harvested 48 h later. DOPAC content in striatum was determined by HPLC, normalized to tissue wet weight and expressed as mean ± s.e.m. **Right panel**. The effect of MPTP on DOPAC expressed as % control for both sexes. BXD40 showed the greatest MPTP-related DOPAC loss for both sexes. ANOVA revealed a significant main effect of strain, sex, treatment ($F_{8,139} = 42.42$, $F_{1,139} = 125.81$, $F_{1,139} = 142.24$, respectively, $p < 0.01$ for each) and significant strain × sex interaction ($F_{8,139} = 24.39$, $p < 0.01$) and strain × treatment interaction ($F_{8,139} = 2.38$, $p < 0.05$), (n = 5 per strain and treatment, b $p < 0.05$, showing significant differences between saline and MPTP treated groups).

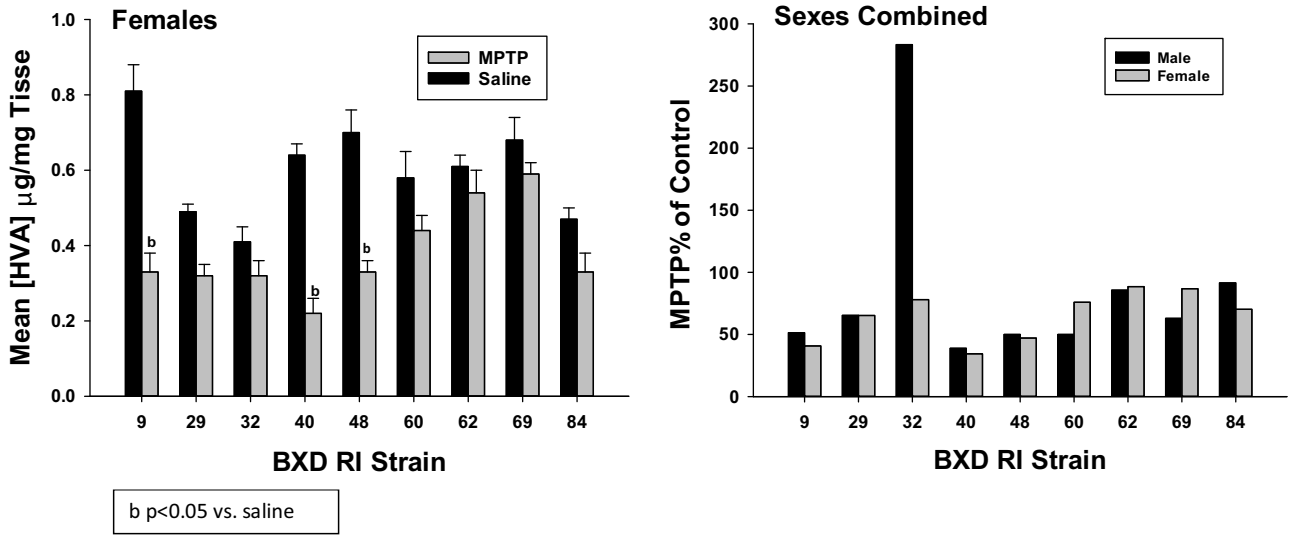

Fig. 3. Left panel. Effect of MPTP on homovanillic acid (HVA) concentration in the striatum in females. The mice were injected with12.5 mg/kg MPTP or saline and tissue harvested 48 h later. HVA content in striatum was determined by HPLC, normalized to tissue wet weight and expressed as mean ± s.e.m. Significant differences in basal levels of HVA were observed with strain BXD32 and BXD9 having the lowest and highest HVA concentration in females respectively. **Right panel**. The effect of MPTP on HVA expressed as % control in both sexes. BXD 40 showed the greatest reduction in both sexes. ANOVA revealed a significant main effect for strain and treatment ($F_{8,140} = 11.49$, $F_{1,140} = 111.26$ respectively, $p < 0.01$ for each). ANOVA revealed a significant strain × treatment interaction ($F_{8,140} = 6.70$, $p < 0.01$), (n = 5 per strain and treatment, b $p < 0.05$, showing significant differences between saline and MPTP treated groups).

interaction was significant. Strain × treatment, sex × treatment and strain × sex × treatment interactions were not significant. The percent of control (MPTP vs. saline) of striatal HVA/DA for both sexes is shown in Fig. 4, right panel.

3.1.5. Effects of MPTP on DA turnover (HVA/DA)

In females BXD69 and BXD9 showed the lowest and highest basal levels for HVA/DA respectively (Fig. 5 left panel). ANOVA revealed significant main effects for strain, sex and treatment. The sex × strain, strain × treatment, treatment × sex and strain × sex × treatment interactions were also significant. The percent of control (MPTP vs. saline) for HVA/DA in the striatum in both sexes is shown in Fig. 5 (right panel). With the exception of strains 32 and 40, there was good consistency between the sexes.

3.2. Effects of MPTP on serotonin (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA)

ANOVA revealed significant main effects for strain with BXD69 and BXD84 having the lowest basal levels of 5-HT and BXD48 the highest 5-HT basal level in females (data not presented). We observed small but significant effects by omnibus F for treatment, and sex on 5HT; however, post hoc tests showed no differences between saline and MPTP across the strains. There was no significant effect of MPTP on 5-HIAA.

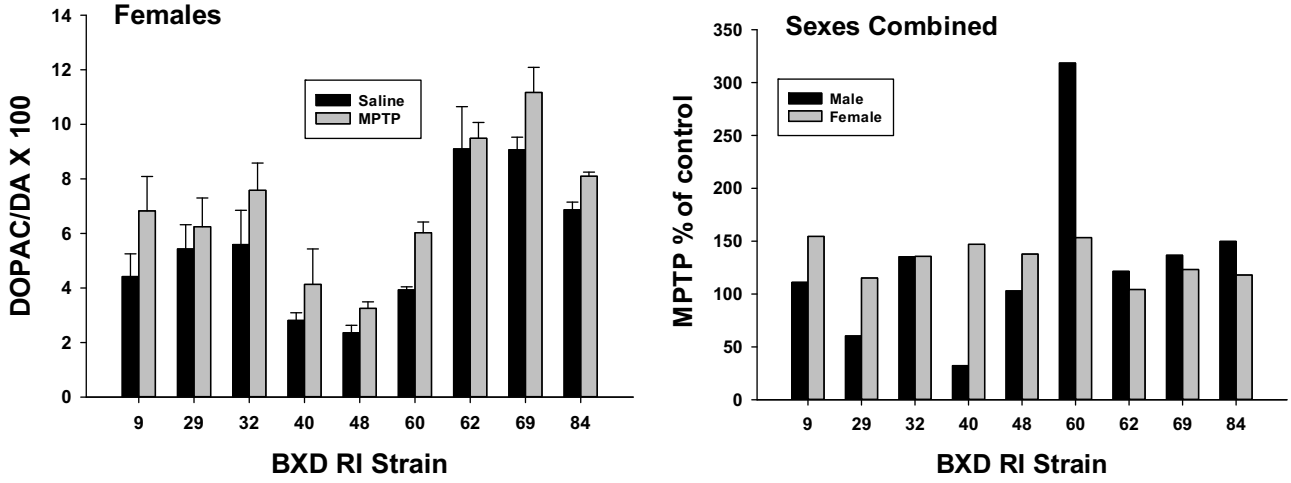

Fig. 4. Left panel. Effect of MPTP on DA turnover as determined by the ratio of DOPAC/DA in the striatum in female BXD mice. Mice were injected with 12.5 mg/kg MPTP (vs. saline) and tissue harvested 48 h later. Experimental and control values normalized to tissue wet weight are expressed as mean ± s.e.m. **Right panel**. The effect of MPTP on DOPAC/DA expressed as% control for both sexes. ANOVA revealed significant main effects for strain, sex and treatment ($F_{8,140} = 4.42$, $F_{1,140} = 13.11$, $F_{1,140} = 6.98$ respectively, $p < 0.01$ for each), and significant effect for strain × sex interaction ($F_{8,140} = 3.62$, $p < 0.01$). (n = 5 per strain and treatment, b $p < 0.05$, showing significant differences between saline and MPTP treated groups).

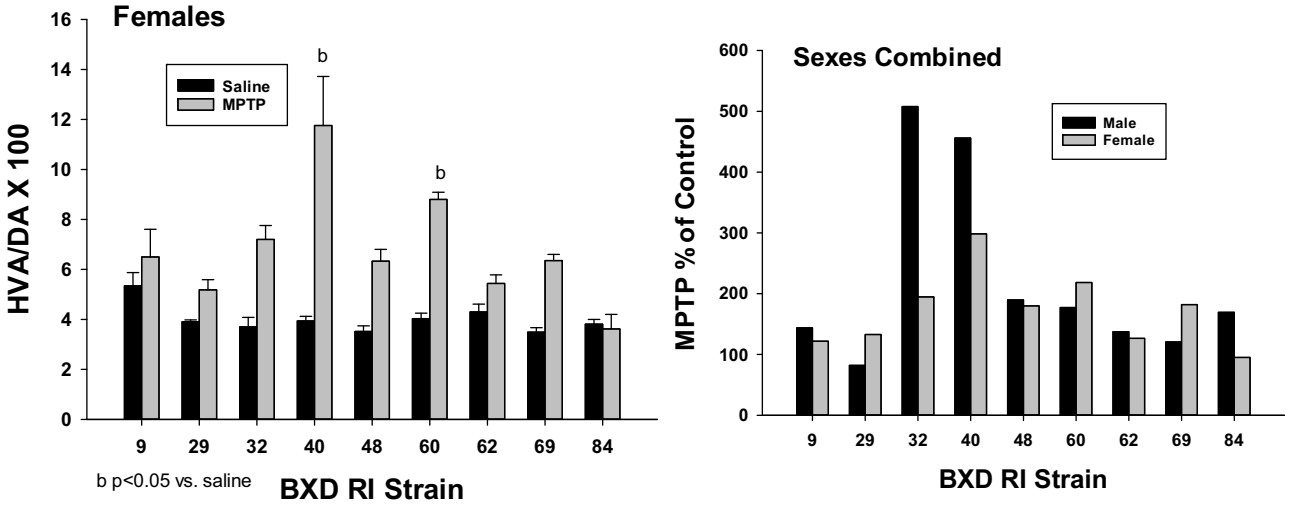

Fig. 5. Left panel. Effect of MPTP on DA turnover as determined by the ratio of HVA/DA in the striatum of female BXD RI mice. Female mice were injected with 12.5 mg/kg MPTP (vs. saline) and tissue harvested 48 h later. Experimental and control values normalized to tissue wet weight are expressed as mean ± s.e.m. **Right panel.** The effect of MPTP on HVA/DA expressed as % control in both sexes. ANOVA revealed significant main effects for strain, sex and treatment ($F_{8,140} = 24.48$, $F_{1,140} = 8.53$, $F_{1,140} = 128.89$ respectively, $p < 0.01$ for each).The sex × strain, strain × treatment, and strain × sex × treatment interactions were significant ($F_{8,140} = 8.99$, $F_{8,140} = 19.97$, $F_{8,140} = 5.33$, $p < 0.01$ for each). The sex × treatment interaction was also significant ($F_{1,140} = 4.64$, $p < 0.05$), (n = 5 per strain and treatment, b $p < 0.05$, showing significant differences between saline and MPTP treated groups).

3.3. Effects of MPTP on tyrosine hydroxylase (TH)

ANOVA revealed significant main effects in basal level by strain with BXD29 and BXD9 having the lowest and highest values, respectively in females (Fig. 6 left panel). We observed significant main effects for treatment. The main effect for sex was not significant. The Sex × strain, strain × treatment, sex × treatment and sex × treatment × strain interactions were all significant. Percent of control (MPTP-saline) for TH in both sexes is shown in the right panel with BXD62 showing the lowest TH loss in both sexes and BXD40 showing the highest loss in both sexes (Fig. 6, right panel).

3.4. Effects of MPTP on GFAP in the striatum

Fig. 7 (left panel) shows that overall, MPTP increased protein expression of the astrocyte marker, GFAP. ANOVA revealed significant main effects for strain with BXD48 and BXD29 having the lowest and highest basal levels, respectively, of GFAP in females. For sexes combined (Fig. 7, right panel), the strain by

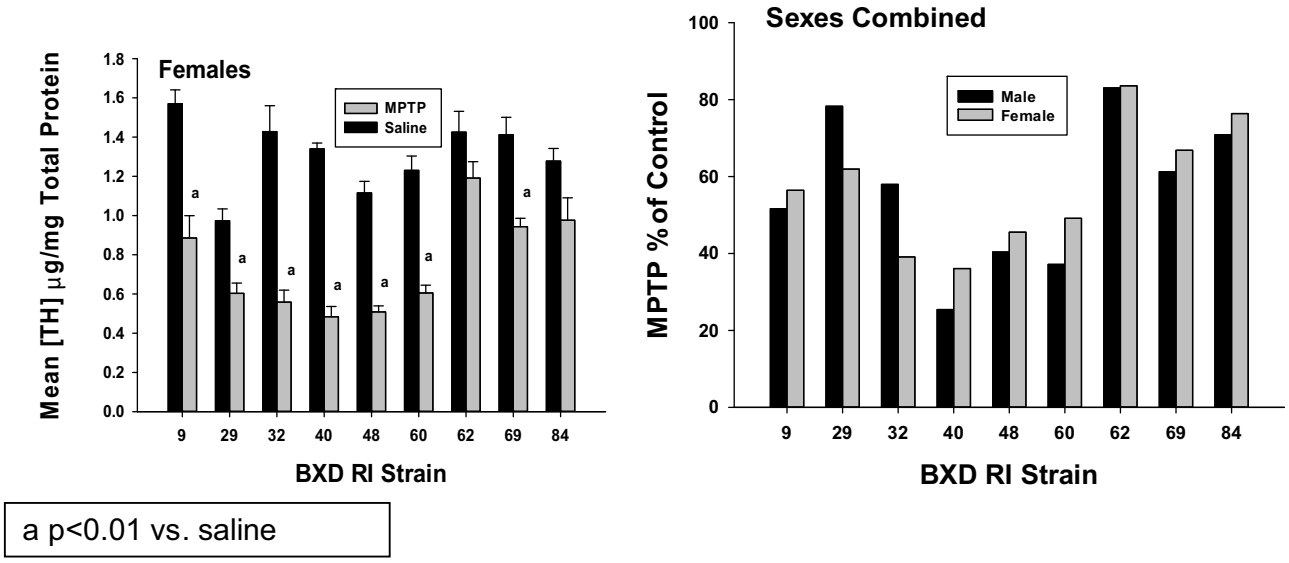

Fig. 6. Left panel. The effects of MPTP on tyrosine hydroxylase (TH) concentration in the striatum in females. Mice were injected with 12.5 mg/kg MPTP (vs. saline) and tissue harvested 48 h later. TH content was determined by sandwich ELISA according to the method of O'Callaghan (1991) and normalized to total protein. Data are expressed as mean ± s.e.m. **Right panel**. Effect of MPTP on TH expressed as % control in both sexes. ANOVA revealed significant main effect of strain and treatment ($F_{8,141} = 19.07$, $F_{1,141} = 641.67$, $p < 0.01$ for each). Sex × strain, strain × treatment and sex × treatment interactions were all significant ($F_{8,141} = 5.71$, $F_{8,141} = 14.40$, $F_{1,141} = 9.85$, $p < 0.01$ for each). The sex × treatment × strain interaction was also significant ($F_{8,141} = 3.31$, $p < 0.05$), (n = 5 per strain and treatment, a $p < 0.05$, showing significant differences between saline and MPTP treated groups).

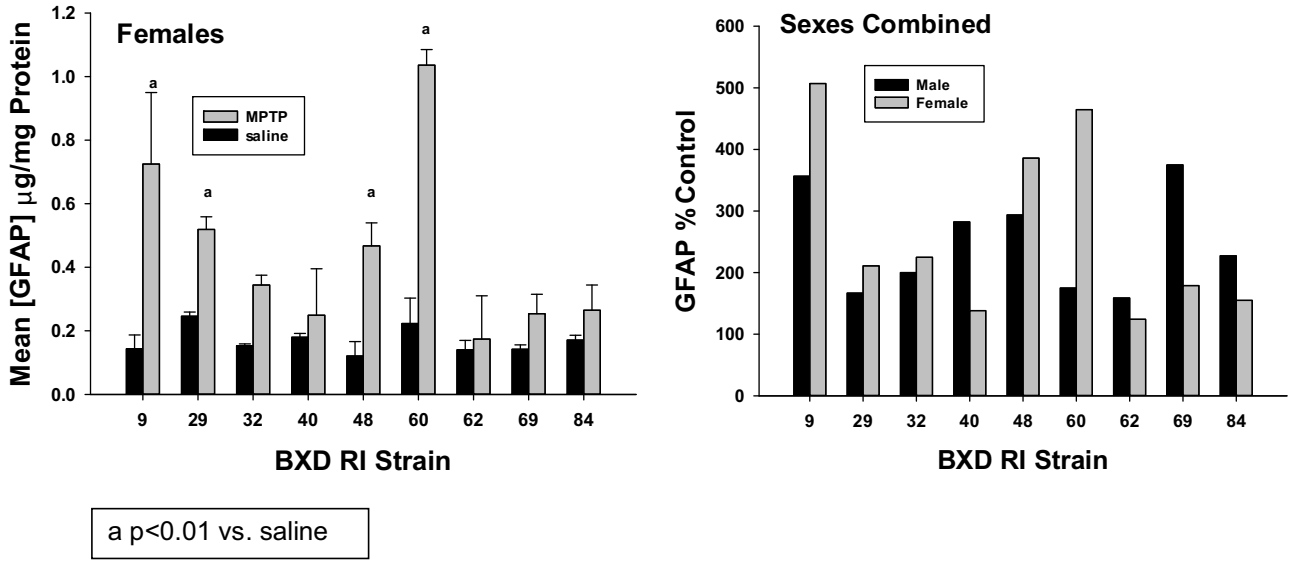

Fig. 7. Left panel. Effect of MPTP on the concentration of glial fibrillary acidic protein (GFAP) in the striatum in females. The mice were injected with 12.5 mg/kg MPTP (vs. saline) and tissue harvested 48 h later. GFAP content was determined by sandwich ELISA (O'Callaghan, 1991; O'Callaghan et al., 2014). GFAP concentrations were normalized to total protein and expressed as mean ± s.e.m. **Right panel.** Effects of MPTP on striatal GFAP expressed as % control in both sexes. ANOVA revealed significant strain, sex and strain × treatment effects ($F_{8,138} = 20.19$, $F_{8,138} = 10.65$, respectively, $p < 0.01$ for each), ($n = 5$ per strain and treatment, a $p < 0.05$, showing significant differences between saline and MPTP treated groups).

treatment effect was significant with BXD69 showing the greatest in males, BXD9 showing the greatest in females and BXD62 showing the least elevation in GFAP concentration in both sexes.

4. Correlational analysis of MPTP effects between the sexes

We observed significant Pearson product-moment correlations between the sexes for DA, HVA and TH (Table 1).

5. Principal component mapping

When performing quantitative trait loci analysis (QTL) with multiple, related endpoints, principal components analysis can reduce the number of related variables to one or more principal components or eigentraits and actually increase the signal for QTL analysis. For this study, we combined mean difference scores across the 9 strains for DA, DOPAC, HVA and TH into one principal component, or eigentrait, that accounted for 70% of the variance. As we found earlier in males (Jones et al., 2013), the eigentrait for the females mapped to chromosome 1 at the same locus, about 60, Mb with a suggestive LOD (Log of Odds) score of about 2.6 (suggestive limit was 2.49). When the data from the sexes were combined, the LOD score for the QTL reached significance at 5.0.

6. Discussion

This is a follow up to our previous study (Jones et al., 2013), in which we examined the effect of host susceptibility to MPTP in male BXD mice. Genetic-based response variation was examined in females from nine of the same strains previously evaluated in males. The agreement in some of the outcomes but not all, between sexes was significant. The correlation for DA measures, except for DOPAC, were significantly high whereas DOPAC and GFAP were not significantly correlated between males and females suggesting possible sex differences in the metabolism of DA and in the astroglial response to dopaminergic neurotoxicity. These differences leave open the possibility for closer investigation of the role of sex in future studies. Because only a limited number of strains were evaluated it remains to be seen if studying a greater number of strains should occur before concluding that sex does not play a role. Also encouraging, is the significant QTL obtained for the DA aggregate response to MPTP. Mapping with only 9–10 strains however, is risky and nomination of candidate genes should await replication with more strains.

DA turnover as indicated by DOPAC/DA showed no evidence of MPTP treatment, whereas HVA/DA was generally increased by MPTP. While the exact mechanism for this is not possible to determine here, it may reflect a decrease in the efficacy of reuptake by the DA transporter (see below). In related work, Ookubo et al. (2009) reported sex differences in MPTP neurotoxicity in C57BL/6 mice. They treated the animals with 20 mg/kg MPTP every 2 h for a total of 4 injections. Four groups were treated in this manner (vs. saline control) and tissues harvested at 5 h, 1, 3, and 7 days. At 5 h, there were no sex differences; however, beginning on day 1, females showed greater and increasing decreases than males in striatal DA and HVA. TH showed greater decreases in both sexes beginning at 5 h with greater loss in females beginning on day 1. For GFAP, females showed greater increases than males beginning at 5 h and continuing to day 3. Comparing to our results, at our dose, we observed good agreement in DA system perturbation between the sexes, but not as much for GFAP. For GFAP, we saw greater increases in females from three of the 9 strains, but greater response in males in two strains. The C57BL/6 strain is one of two founder strains for the BXD recombinant inbred family, DBA/2 being the other. Neither of the parental strains was available to us;

Table 1
Pearson product-moment correlations, males vs. females for difference scores, saline vs. MPTP.

DA	HVA	DOPAC	TH	5-HT	5-HIAA	GFAP
r = 0.80	r = 0.66	r = 0.05	r = 0.79	r = 0.03	r = 0.52	r = 0.20
p < 0.01	p < 0.05	n.s.	p < 0.01	n.s.	n.s.	n.s.

however, the allelic differences between the two were present in our group of 9 RI strains. The effects that we report across the strains show continuous variation and thus additive genetic influence from alleles from multiple genes donated by the parental strains. The point is that sex differences in response to toxicants like MPTP likely depend on genetic constitution as well as dose and dosing conditions. What is also of interest is Ookubo et al. (2009) report a greater decrease in DA transporter protein in females compared to males after 3 days.

MPTP neurotoxicity shows wide, genetic variability with responses showing continuous distributions, indicating the involvement of multiple genes in determining the susceptibility to MPTP toxicity. In other words, host susceptibility is considered to be a polygenic or complex trait, involving several genes that interact with the environment and likely with each other. Systems genetics analysis together with a forward genetics approach (starting with examining phenotypes followed by identifying candidate genes) is a powerful technique to identify underlying mechanisms. As shown here, the combination of several related phenotypes through principal components analysis strengthens the ability to locate and nominate candidate genes.

By using systems genetics, we showed that the extent of MPP+ production was quantitatively unrelated to the extent of DA loss in the striatum and showing once again that MPTP neurotoxicity is highly complex and determined by multiple factors (Jones et al., 2014). There is evidence showing the possible involvement of other enzymes such as mitochondrial cytochrome P450 2D6 (CYP2D6) in addition to monoamine oxidase B (MAOB) in the metabolism of MPTP to MPP+ (Bajpai et al., 2012). These researchers showed that the mitochondrial enzyme CYP2D6 located in the dopaminergic cells of substantia nigra is capable of metabolizing MPTP to MPP+, almost with the same efficiency as MAOB. A future examination of CYP2D6 in BXD RI strains would provide additional insight into the factors controlling the neurotoxic response to MPTP in these strains. The existence of multiple enzymes for the metabolism of MPTP to the active neurotoxic agent MPP+ indicates that MPTP neurotoxicity is a complex trait involving multiple pathways and potentially multiple genes. Examining the effect of CYP2D6 polymorphisms along with other factors such as DA transporter polymorphisms and genetic differences in mitochondrial complex I players will likely shed light on the complex pathways involved in MPTP toxicity.

The results of this study show the existence of a broad response variation concerning MPTP toxicity among different strains of female BXD RI mice which resembles individual differences observed in humans. Mapping these differences enables researchers to pinpoint polymorphisms and candidate genes that may be involved in increased risk for complex phenotypes such as neurotoxicity in general and also neurodegenerative diseases including PD.

7. Conclusion

This study in female BXD mice is a follow up to our previous study in males of the same BXD strains in which we examined the neurotoxic effect of MPTP. We have shown that similar to males, there is a broad range of response variation in the females among BXD strains. Moreover, there is remarkable similarity in the neurotoxic responses to MPTP between the sexes. But, there are some differences and whether these differences stem from measurement or methodological error or represent important biological processes remains to be seen. This work thus sets the stage for more extensive work in many more BXD strains (about 100 exist) or in similar genetic reference populations. Such work will allow include gene mapping and gene expression resulting in the nomination and confirmation of candidate genes. Such studies will aid us in understanding the role of individual differences and genetic background in neurotoxicity and subsequent neurodegeneration.

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