

Evaluation of Constipation Endpoints in MPTP-Treated Mice

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1 BACKGROUND

- Constipation in Parkinson's disease is a significant burden on the patient and is one of the most important non-motor symptoms they need to manage
- Currently, there are not treatments that prevent constipation in PD patients
- Although there has been an increasing awareness of the importance of constipation in PD, there are no universally accepted animal models used to evaluate potential novel treatments
- Recently Ellet *et al.*, 2016 reported that MPTP treated mice have roughly 30% decrease in stool frequency relatively to untreated animals
- The purpose of the present work was to determine if we could reproduce this effect in MPTP treated mice
- Additionally, we assessed motility using a glass bead extrusion assay

2 METHOD

Animals

Male C57Bl6 mice aged 9 weeks were used for the study.

MPTP

MPTP was given twice a day at the dose of 20 mg/kg in saline i.p. at 3-h intervals on two consecutive days (Days -1 and 0), the total amount being then 80 mg/kg. Dosing volume for MPTP was 10 mL/kg and pure MPTP active compound concentration is 2.0 mg/mL (after salt correction factor).

Motility/Output

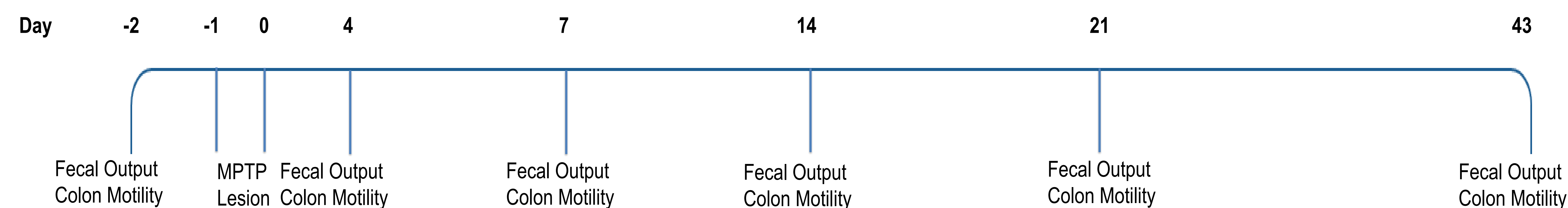
Fecal Output Methods in Brief:

- The animals were fasted 12 h prior to experimentation.
- The mice were placed in locomotor activity chambers for 60 min.
- Following the activity monitoring, fecal pellets were collected, weighed and counted.
- Endpoints were the total weight and number of fecal pellets.

Colon Motility Methods in Brief:

- The animals were fasted 12 h prior to experimentation.
- Colonic motility was assessed by measuring time to extrusion of a single glass bead (2 mm) inserted 2 cm into the distal colon of the mice.
- Extrusion time was determined for each mouse.

3 STUDY DESIGN



Groups

- Sham (n=10)
- MPTP (20 mg/kg, IP; BID) (n=11)

4 OUTCOMES

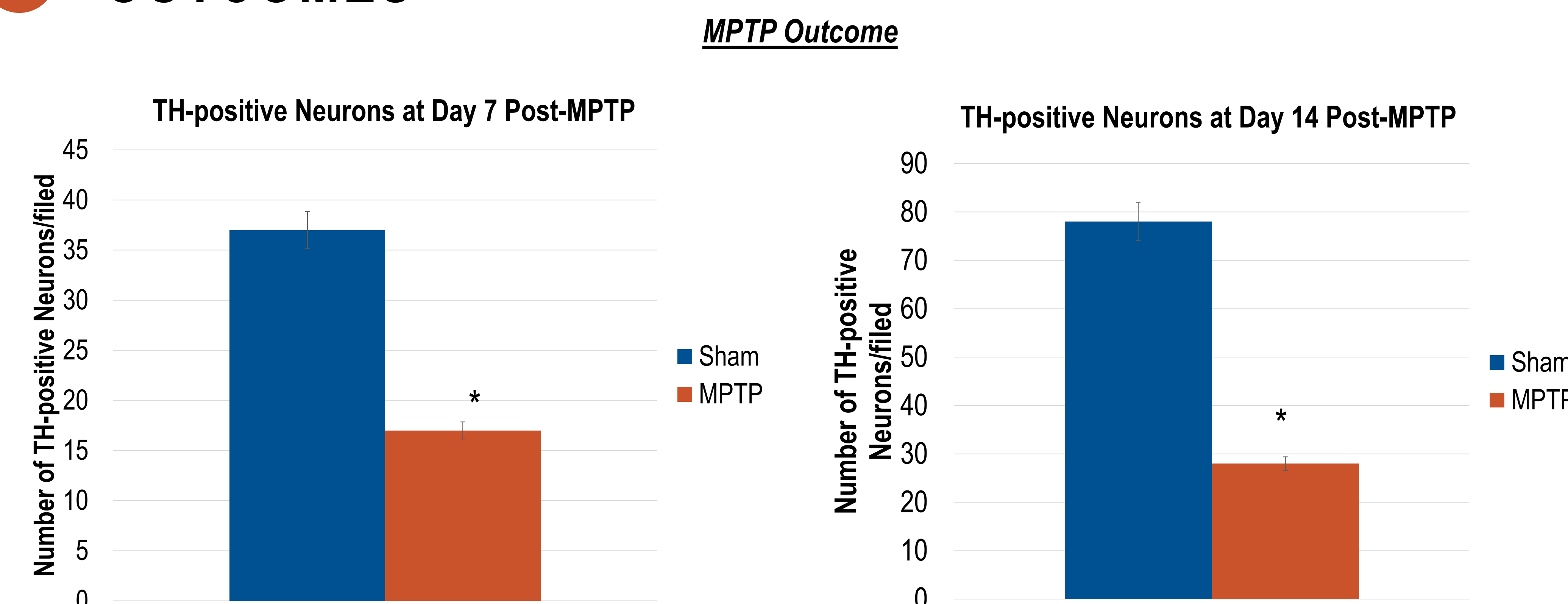


Figure 1. Representative data from our MPTP mouse model. TH reduction is lowered by roughly 50% - 60% by Day 7 (top graph) and by roughly 70% by Day 14. These results are similar to the TH loss reported previously by Ellet *et al.*, 2016.

Dopamine Reduction in Striatum

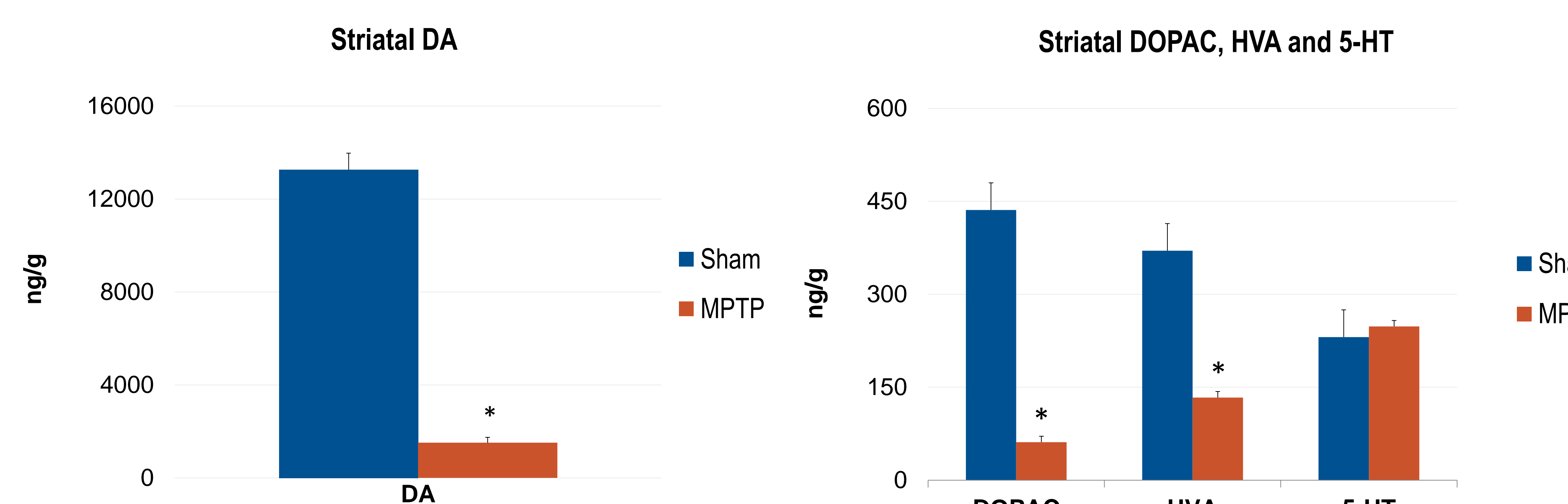


Figure 2. In the MPTP mouse model, DA and its metabolites are significantly reduced as measured post-mortem by HPLC. These results are from a separate group of mice than was used for the constipation measure.

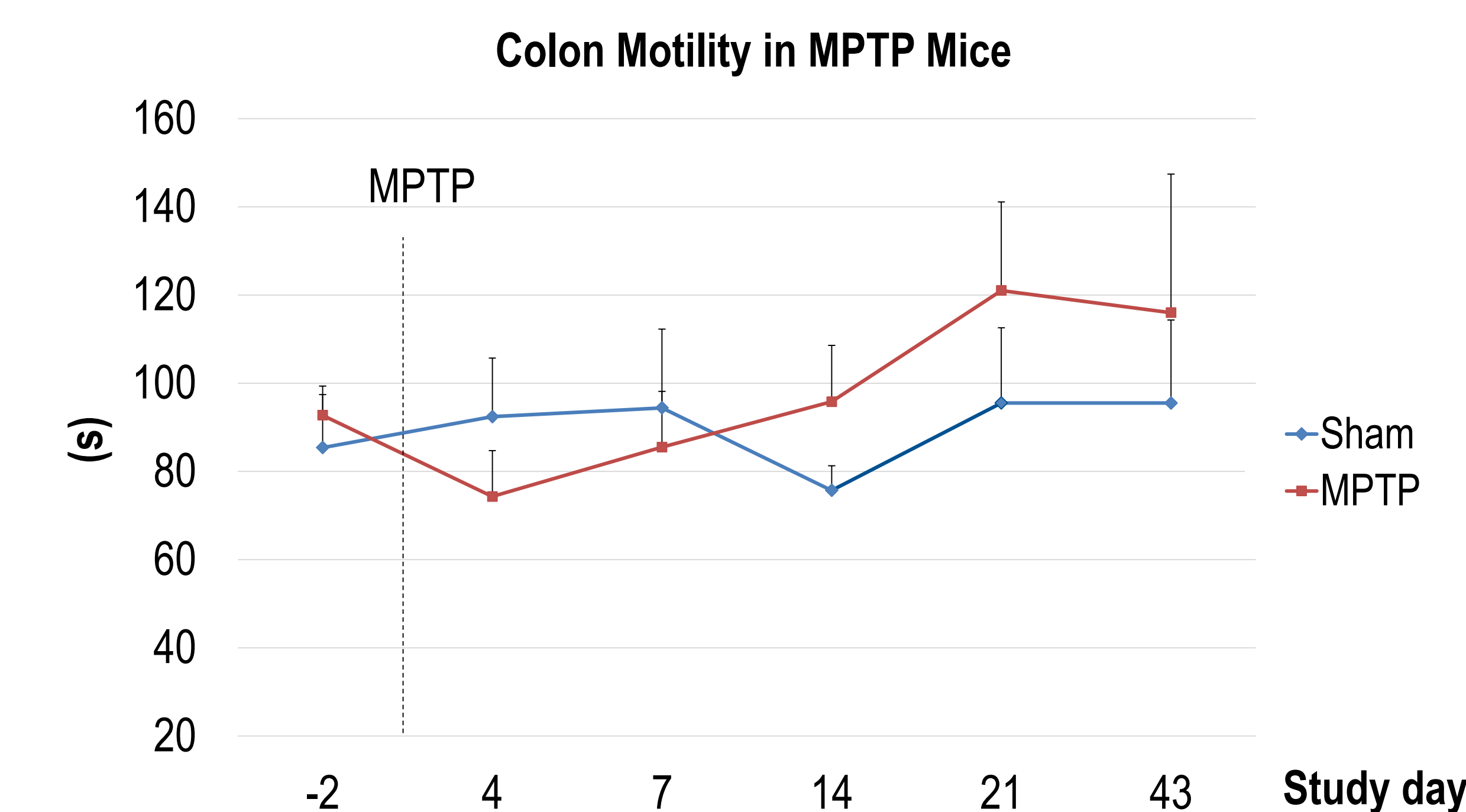


Figure 3. Colon motility as measured by transit time of a rectally inserted glass bead. MPTP treated mice had increasing slower extrusion times as the study progressed. By Day 43, there was a trend in the anticipated direction; MPTP treated mice had slower extrusion time than sham treated ($p=0.16$). $N=10$ per group. Data are represented as mean \pm SEM.

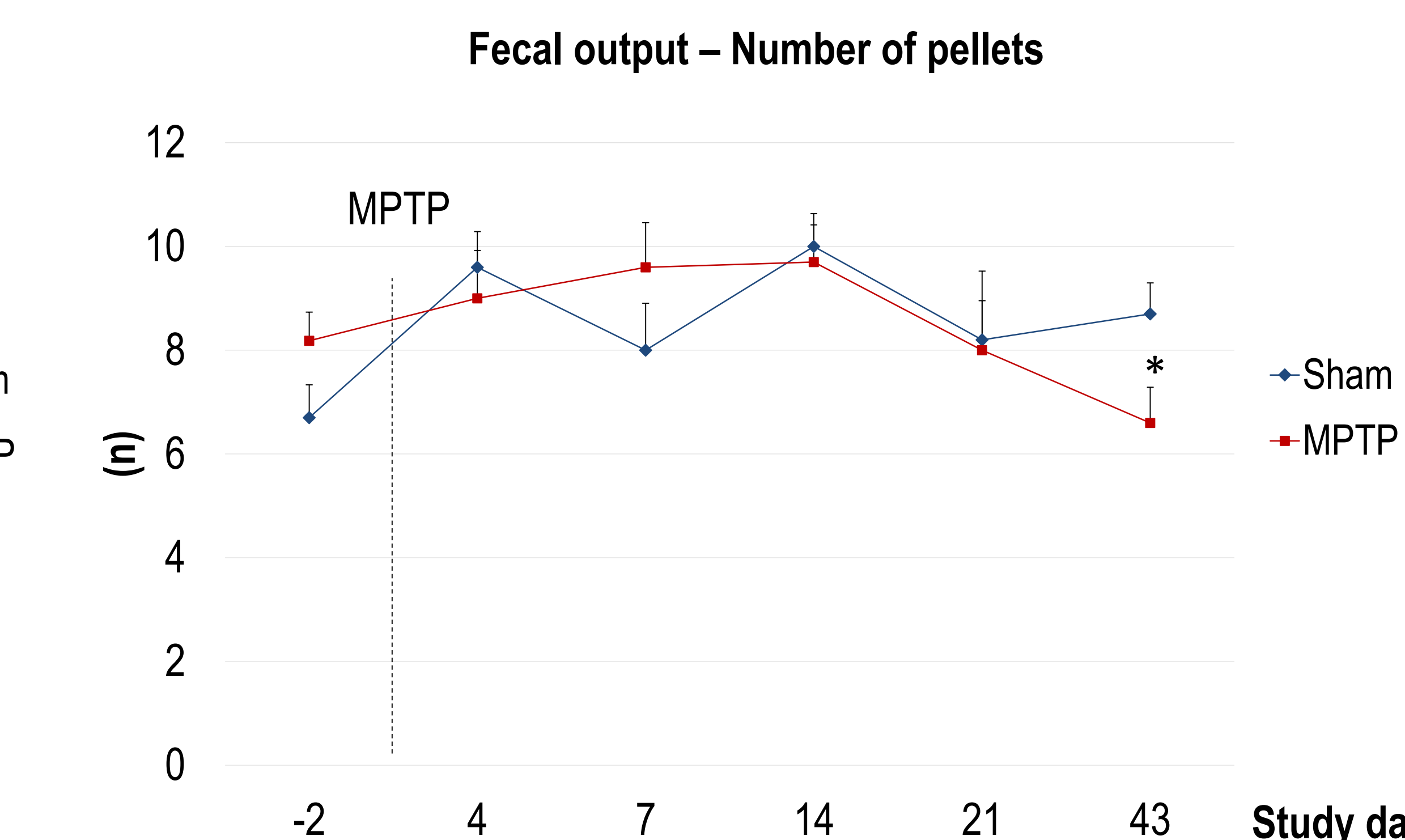


Figure 4. Fecal output was significantly reduced in MPTP treated mice relative to sham operated ($p=.01$). However this effect was only apparent 6 weeks after MPTP treatment. $N=10$ per group. Data are represented as mean \pm SEM.

5 CONCLUSIONS

- Constipation in PD remains a significant issue that is not treated by current PD medications
- Research into novel potential treatments will require animal models that recapitulate the loss of motility in PD patients
- Here we assessed the viability of the MPTP mouse model as a viable mouse model for constipation in PD
- Using the glass bead test, we found that MPTP mice have a reduction in motility that trended towards significance. This effect continue to develop in the weeks following MPTP administration
- There was a modest, but statistically significant reduction in fecal output, consistent with the Ellet *et al.* findings in magnitude
- These results are promising that MPTP delivery to mice may create a viable model for constipation in PD, however further work to optimize the MPTP treatment regimen is needed