Translational Contract Research

Parkinson's disease – MPTP-lesioned mouse

Systemic administration of MPTP to C57bl/6 mice induces a rapid degeneration of dopaminergic neurons within the substantia nigra. This robust and well-characterised model is amenable to a variety of disease-modification study designs and allows for rapid evaluation of test compounds.

Well characterised mouse model of Parkinson's disease

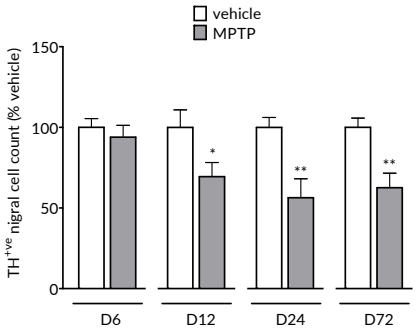
Robust and reproducible model

Allows for rapid evaluation of disease-modifying potential of test compounds

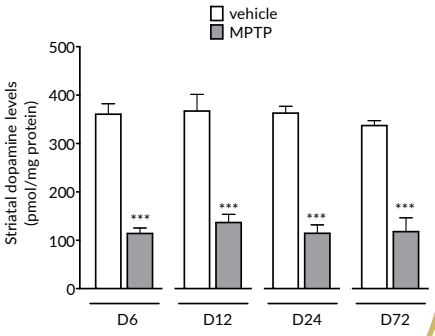
Model overview

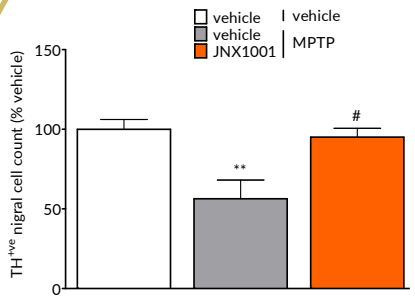
Various iterations of the MPTP-lesioned mouse are offered by Atuka. In one of our most commonly used models, MPTP (25 mg/kg, *i.p.*) is administered to C57bl/6 mice once daily for 5 days. This leads to a loss of tyrosine hydroxylase positive neurons in the substantia nigra that is stable over a period of weeks. Test compounds can be administered alongside MPTP (neuroprotective) or after MPTP (neurorestorative).

MPTP induces a robust and stable dopaminergic lesion

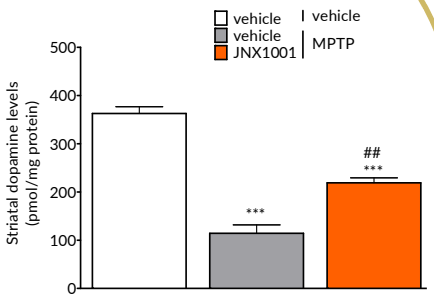


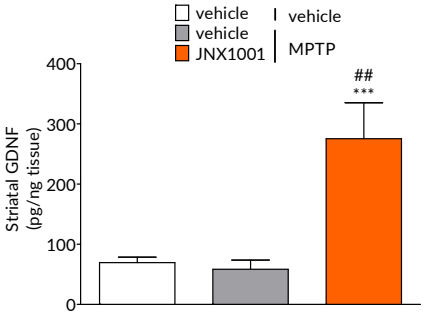
MPTP produces a significant reduction of tyrosine hydroxylase positive cells in the substantia nigra (left) and striatal dopamine levels (right). The loss in striatal dopamine is maximal by Day 6 and is stable up to Day 72. The loss of tyrosine hydroxylase positive cells is slower to develop and is maximal by Day 24 and maintained out to Day 72.



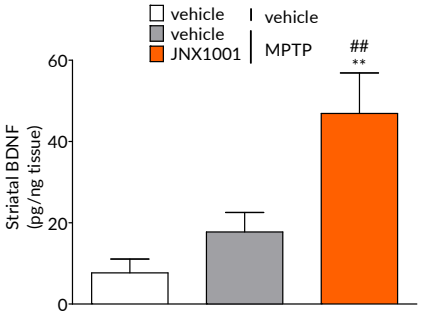


MPTP-induced deficits are reversed by pharmacological treatment. MPTP-induced reductions in tyrosine hydroxylase positive cells in the substantia nigra (left) and striatal dopamine levels (right) are prevented by treatment with JNX1001, a compound that increases GDNF and BDNF production.





Client-specified endpoints allow demonstration of target engagement. In MPTP-lesioned mice, JNX1001 was demonstrated to increase striatal GDNF and BDNF levels demonstrating that JNX1001 was engaging its proposed mechanism of action and providing a rationale behind its protective and restorative effects.



Experimental readouts

Post-mortem **-** Routine post mortem analyses include striatal dopamine and dopamine transporter (DAT) levels and the number of number of TH^{+ve} cells in the substantia nigra. Additional post-mortem measures can be incorporated at the request of the client.

Target engagement **–** Demonstration of target engagement can often be incorporated into the study design aiding translation from rodent studies to non-human primate studies and ultimately to clinical studies.

Imaging **-** We offer both MRI and PET imaging that allows longitudinal measurement of markers of dopaminergic function and metabolism.

Pharmacokinetics- Can be incorporated into all studies. Blood and CSF can be sampled throughout the study and terminal samples of brain and other tissues can be collected.

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