Energy Metabolism-Parkin Link in Methamphetamine Use Disorder

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Introduction

In the height of the opioid crisis in our country, deaths from methamphetamine (METH) overdose are on the rise. Despite numerous preclinical and clinical research efforts, there is no FDA-approved medication for METH use disorder (MUD). New drug targets are need to develop new medications for this disorder, especially for people who use METH heavily and, therefore, are at high risk for an overdose. We previously determined that protein parkin was a novel potential drug target for decreasing heavy use of METH[1] (Fig.1). Parkin is a neuroprotective protein-ubiquitin ligase known to play a critical role in maintaining mitochondrial homeostasis[2]. The goal of the present study was to elucidate molecular mechanisms underlying parkin-mediated regulation of METH taking and to assess whether parkin downregulates METH seeking during a relapse.

Methods

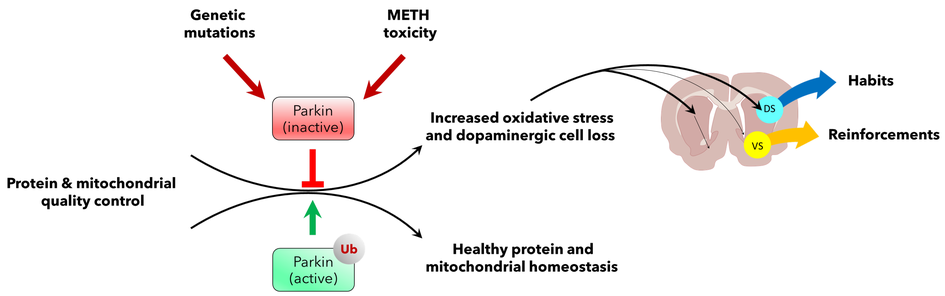
Parkin Overexpression: Male Long Evans 2-month-old rats were bilaterally microinjected with 1.5µL of hParkin-encoding AAV2 vector (~6.5×10^7 TUs/side) into the nucleus accumbens (NAc) at the following co-ordinates: +1.8mm anteroposterior (A/P), ±3.2mm mediolateral (M/L), and −7.6mm dorsoventral (D/V) relative to Bregma, at a 16º angle.

Proteomics: Label-Free Quantitation was performed on a Thermo Scientific Orbitrap Fusion Mass spectrometer connected to a Waters nanoACQUITY UPLC system. The LC-MS/MS data was processed with Progenesis QI software (Nonlinear Dynamics, version 4.2) with protein identification carried out using an in-house Mascot search engine (v2.8). The p value was set at 0.05; FDR was set at 1%. The data was analyzed using Gene Set Enrichment Analysis (GSEA).

Extended-access Methamphetamine Self-administration (EA METH SA): Catheterized parkin knockout (*Park2*$^{-/-}$, PKO), wild-type (WT), and parkin overexpressing (PO) rats were trained to self-administer (+)-METH (0.1mg/kg/injection) and then given access to the drug during 15h-long sessions (6pm-9am) for 10 consecutive days on an increasing fixed-ratio (FR) schedule: FR1 (days 1-3), FR2 (days 4-6), and FR5 (days 7-10). METH relapse was induced on the 10d of withdrawal with 1mg/kg METH. The data was analyzed by ANOVA t-test*p<0.5. **p<0.01, ***p<0.001.

Hypothesis

Parkin-mediated NAc protection from oxidative stress has a role in MUD



Results

Fig.1 Parkin Decreases METH Self-Administration

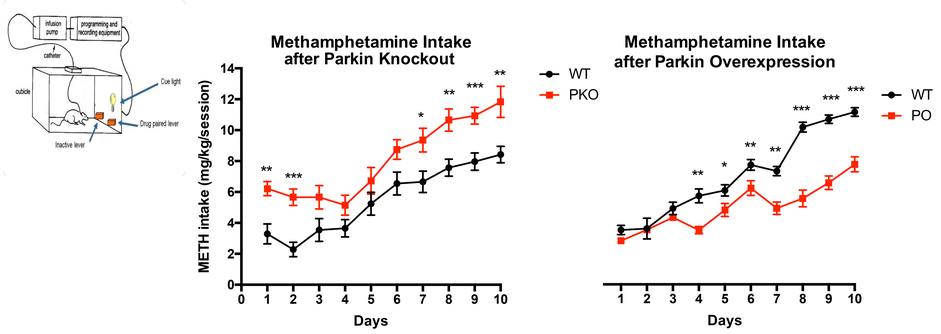
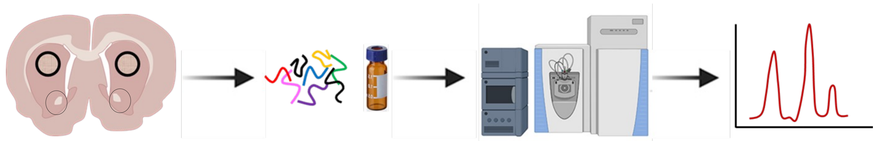
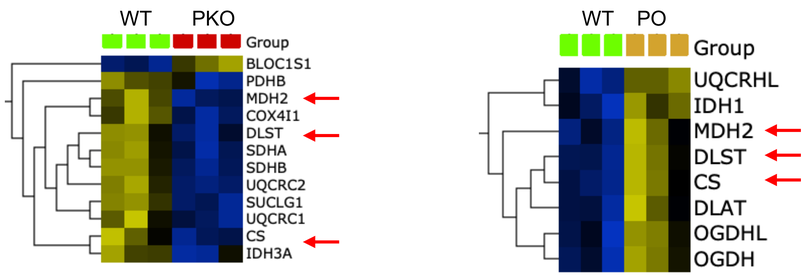


Fig.2 Parkin Alters Krebs Cycle Enzyme Levels in the NAc



Name	Group	Size	Matches	ES	abs(ES)	NES	p	q
GOBP_AEROBIC_RESPIRATION	PKO	86	39	-0.571362	0.571362	-1.89876	0.00385356	0.123771
GOBP_AEROBIC_RESPIRATION	PO	86	39	0.563767	0.563767	1.78061	0	0.0515795
GOBP_ENERGY_DERIVATION_BY_OXIDATION_OF_ORGANIC_COMPOUNDS	PKO	278	79	-0.515965	0.515965	-1.9527	0	0.0835003
GOBP_ENERGY_DERIVATION_BY_OXIDATION_OF_ORGANIC_COMPOUNDS	PO	278	79	0.453966	0.453966	1.62768	0.0052356	0.210268
GOBP_TRICARBOXYLIC_ACID_CYCLE	PKO	34	24	-0.70233	0.70233	-2.11393	0	0.0310919
GOBP_TRICARBOXYLIC_ACID_CYCLE	PO	34	24	0.617922	0.617922	1.80564	0.00145349	0.0455609

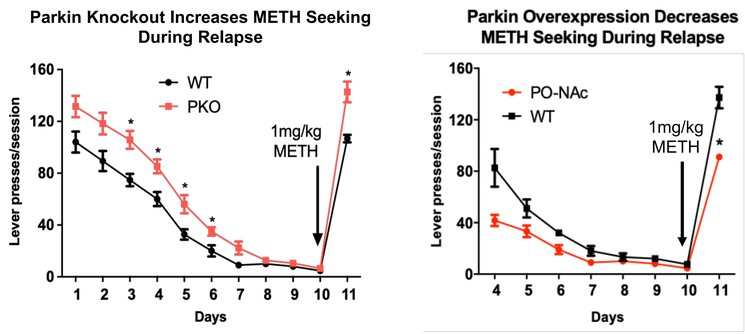


	PKO	PO-NAc
Aerobic respiration	↓	↑
Krebs cycle	↓	↑
Oxidative phosphorylation	↓	=

Fig.3 Parkin Alters ETC Levels in the DLS

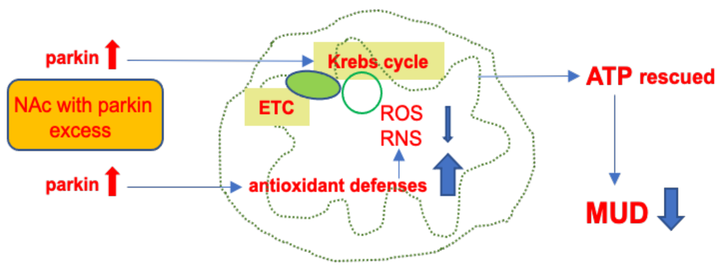
	PKO	PO-DLS
Aerobic respiration	↓	↑
Krebs cycle	=	=
Oxidative phosphorylation	↓	↑

Fig.4 Parkin Decreases METH Seeking



Major Conclusion

Changes in mitochondrial energy metabolism in striatal subregions underlie parkin-mediated regulation of METH taking and seeking during METH-induced relapse.



References

1. Sharma *et al.* Transl Psychiatry. 2021,**17**;11(1):293.
2. Pisl & Winklhofer.Acta Neuropathol. 2012,123(2):173

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