

Phenylbutyrate increases plasma and brain DJ-1 as it prevents behavioral deterioration in a transgenic mouse model of Parkinson's disease

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ABSTRACT

Parkinson's disease is caused by the loss of dopamine neurons in the ventral midbrain. People with mutations in the DJ-1 gene that prevent DJ-1 protein dimerization will develop early onset Parkinson's. We have shown that overexpression of DJ-1 can protect dopamine neurons from oxidative stress by selective upregulation of glutathione (GSH) biosynthesis. If cells are stressed by mutant α -synuclein accumulation, GSH is not increased; instead, heat shock protein 70 production is turned on. We have found that sodium phenylbutyrate (PB) can increase DJ-1 expression by 200-400% in dopamine cell cultures. Using our Y39C mutant α -synuclein transgenic mouse model, we have found that PB treatment for 3 months in aging animals (15-18 months) prevented a decline in motor function by increasing brain and plasma DJ-1 concentrations. Plasma DJ-1 was increased from 3.1 ± 0.3 ng/ml to 6.5 ± 0.6 ng/ml with a PB dose of 1 mg/ml in the drinking water ($p < 0.01$). Increasing PB to 2 mg/ml did not further increase plasma DJ-1. We conclude that phenylbutyrate can upregulate DJ-1 activity and prevent progression of motor complications in a transgenic mouse model of Parkinson's disease. Based on these data, we have initiated a clinical trial of phenylbutyrate in patients with Parkinson's disease.

Supported by: The Coleman Institute for Cognitive Disabilities, The Parkinson Disease Foundation, The Michael J. Fox Foundation, and gifts from Charles and Joanne Ackerman. Wenbo Zhou, PhD, is a Coleman Institute Fellow.

INTRODUCTION

Histones can be post-translationally modified by enzymes that covalently add or remove a number of different chemical modifications, including acetyl, phosphate and methyl groups.

The acetylation of key lysine residues of histone H3 and H4 by enzymes known as histone acetyltransferases (HATs) has long been known to play a pivotal role in transcriptional activation.

Conversely, the removal of the acetyl groups by enzymes known as histone deacetylases (HDACs) is known to lead to transcriptionally inactive chromatin.

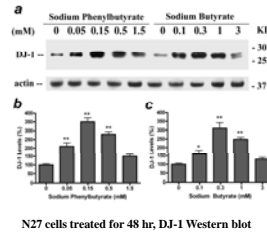
HDAC Inhibitors (HDACi) have shown benefit in animal models of Huntington's disease, spinal muscular atrophy, and amyotrophic lateral sclerosis.

HDACi have been reported to prolong survival of neurons and increase anti-apoptotic gene expression.

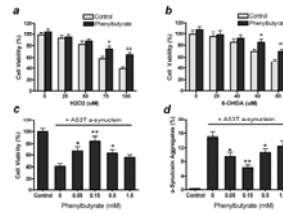
Phenylbutyrate, an HDACi, can prevent dopamine neuron death in the MPTP mouse model of Parkinson's.

RESULTS

1 Butyrate and Phenylbutyrate increase DJ-1 expression in N27 cells

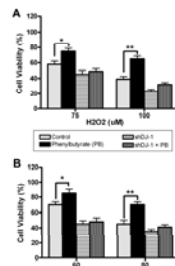


2 Phenylbutyrate protects against oxidative stress and α -synuclein-induced cell death in N27 cells

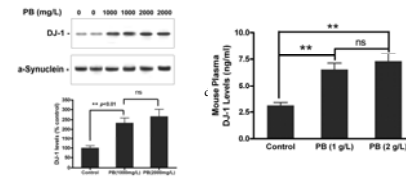


PB Treatment for 48 hr, Oxidative stress for 24 hr, MTT assays.
PB - induced DJ-1 plays a critical role in defending cells from oxidative stress

3 Knocking-down DJ-1 blocks beneficial effects of Phenylbutyrate

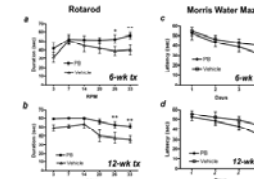


4 Phenylbutyrate increases brain DJ-1 and plasma DJ-1 levels in adult mice



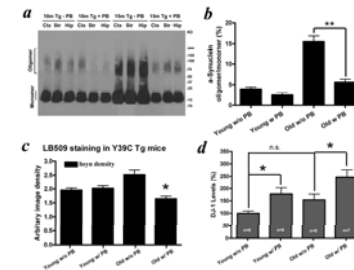
Phenylbutyrate in drinking water for one week.
Left panel shows brain cortex analyzed by Western blotting with DJ-1 antibody, Right panel shows blood plasma DJ-1 measured by ELISA.

5 Phenylbutyrate improves behavior in aged mutant- α -synuclein mice



15 month old Y39C- α -syn transgenic mice were treated with PB or vehicle for 6 or 12 weeks

6 Phenylbutyrate reduces synuclein aggregation by increasing DJ-1 in transgenic mice



CONCLUSIONS

- Phenylbutyrate can increase brain and plasma concentrations of the neuroprotective protein DJ-1.
- Treatment with phenylbutyrate can prevent the age-related decline in motor and cognitive function in old transgenic mice.
- Phenylbutyrate-induced DJ-1 improves brain function by preventing alpha-synuclein aggregation.
- In humans, treatment with phenylbutyrate may stop progression of Parkinson's disease.