Astaxanthin Attenuates Neurotoxicity in a Mouse Model of Parkinson's disease

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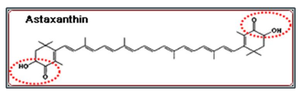
Major Findings

- Astaxanthin (AXT) prevents neuron loss after exposure to MPTP
- AXT reduces microglial response to MPTP neurotoxicity
- AXT increases glutathione
- AXT may be acting as both an antioxidant and anti-inflammatory to attenuate neurotoxicity of MPTP.
- Promising therapeutic agent for the treatment of PD

Background



Astaxanthin (AXT) is a xanthophyll carotenoid produced by the marine algae *Heamatococcus Pluvialis.* AXT has multiple putative mechanisms of action that are relevant to pathophysiology that underlies Parkinson's disease, indicating a distinct and promising therapeutic potential in the treatment and management of symptoms in PD patients.

AXT is best known for its potent antioxidant activity, reported to be much more effective than other compounds in its class. This is likely due to the numerous actions as an antioxidant, as it can reduce radicals by absorption, donation of electrons, and formations of adducts with the reactive species. Polar ionone rings cap the carbon backbone, distinguishing the molecule from other carotenoids, and allows AXT energetically favorable spanning the phospholipid bilayer of cell membranes, protecting the membrane against lipid peroxidation

AXT has also been implicated in modulating the immune response *in vitro*, indicating a potential anti-inflammatory action for this compound. Studies demonstrate that astaxanthin can reduce the expression of IL-6 and iNOS/NO in microglia when exposed to an endotoxin like LPS .These results were corroborated by *in vivo* experiments where AXT reduced the release of nitric oxide . These molecules are released in high amounts by activated microglia and are associated with neuronal damage.

AXT prevents MPTP induced neurodegeneration

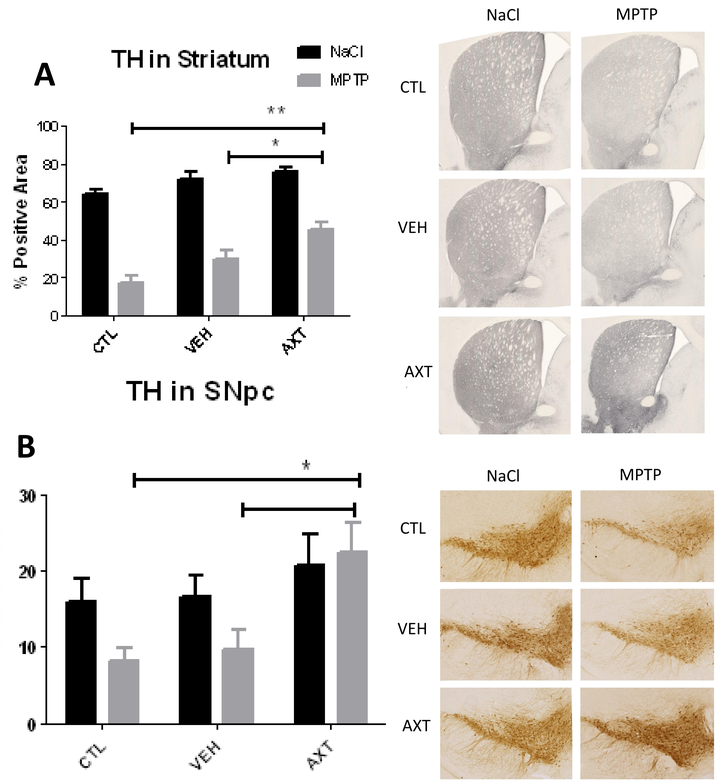


Figure 1: A 1 month dietary treatment of astaxanthin preserves TH immunoreactivity in both the striatum and the substantia nigra pars compacta in response to MPTP neurotoxin. A) ** p<.001, * p<.05 B) * p<.05 C) Dietary intervention of astaxanthin preserves NeuN staining in the substantia nigra pars compacta in response to MPTP neurotoxin (p<.05).

AXT alters microglial response to MPTP neurotoxicity

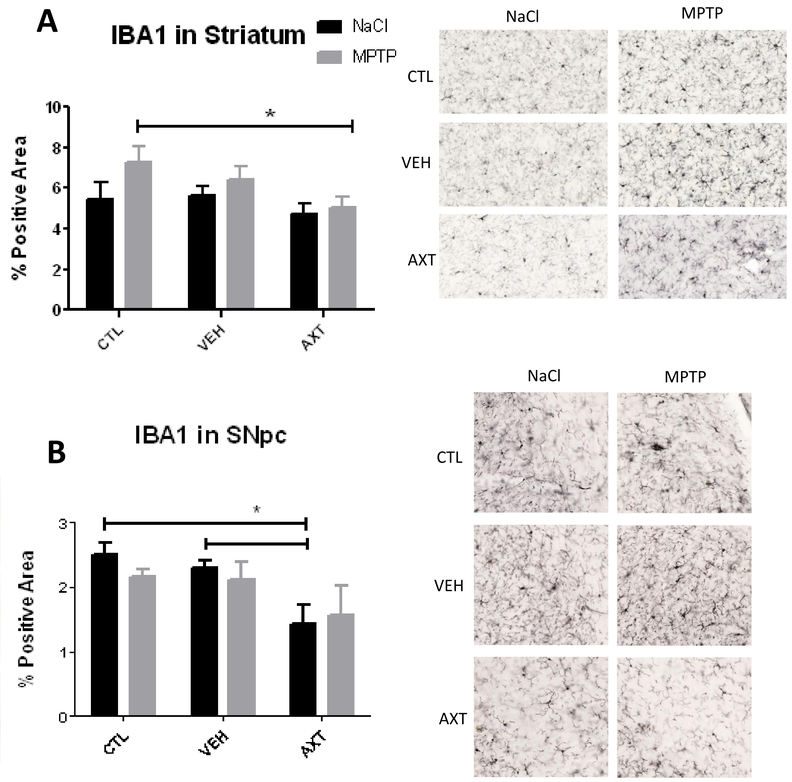


Figure 2: Dietary intervention of astaxanthin modulates microglial response to the neurodegeneration that results from MPTP neurotoxicity. A) MPTP induced upregulation of the microglial marker IBA1 is attenuated in the striatum of mice being treated with AXT (p< .05). B) Similar trends were observed in the substantia nigra pars compacta. IBA1 expression is reduced by dietary intervention (p< .05).

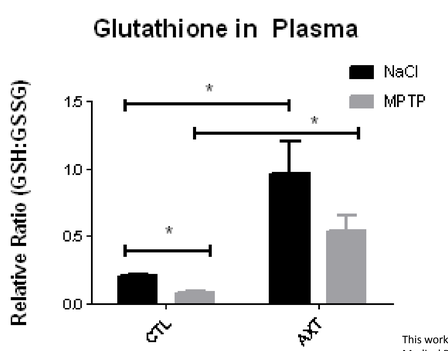


Figure 3: Astaxanthin increases the ratio of reduced glutathione(GSH) to oxidized glutathione (GSSG). There is a main effect of AXT alone. Although MPTP still reduces glutathione in the AXT group the levels remain higher than baseline control (*p<.05).

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Conclusions

Here, we demonstrate that a one month dietary intervention with AXT can reduce neurodegeneration in response to MPTP toxicity. We show that AXT treated mice retain TH immunoreactivity in both the substantia nigra and the striatum 7 days after exposure to the neurotoxin. These results were corroborated by preserved NeuN in the substantia nigra, indicating more neurons in this region survived the insult. We have also observed a dietary effect on the expression of IBA-1 in both the substantia nigra and the striatum, indicating a modulatory role in neuroimmune function and microglial activity. Finally, we observed that a dietary treatment with AXT can regulate levels of glutathione in the plasma. Taken together, these data suggest a therapeutic potential for astaxanthin in the development or progression of Parkinson's Disease symptoms.

Methods

Dietary intervention: Mice were treated with 3 mg/kg of Bioastin® generously supplied by Cyanotech. This is a natural astaxanthin product delivered on inert cellulose beads with trace amounts of vitamin E. For this reason, we included a separate group treated with the empty beads to serve as a vehicle control. These compounds were delivered in an NIH-31, ad libitum, 1 month prior to MPTP administration. Food intake per cage and body weights were monitored throughout the course of treatment to ensure consumption.

MPTP administration: The MPTP HCL was diluted in sterile saline and injected intraperitoneally. The mice received four injections at a dose of 10 mg/kg, administered once per hour four hours for a final dose of 40 mg/kg MPTP or equal volumes of sterile saline. Mice were transcardially perfused 7 days after MPTP injections.

Immunohistochemistry: 40 µM coronal sections were selected at a periodicity of 1 in 6 for all IHC procedure. Free floating sections were incubated in primary antibody diluted in serum and TX-100 for 24 hours at 4º and secondary antibody for 60 minutes at 25 º. After incubation in avidin-biotin complex, stains were developed with DAB.

Quantification: immunoreactivity was quantified using an axioscan microscope (20X objective) and NearCYTE image analysis software. This program applies a user defined threshold of color intensity to images of the sections and generates a ratio of positive staining within a region of interest.

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