U.S. Food and Drug Administration
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FDA Cross Comparison Study: Four Nrf2 Activators in the Treatment of Multiple Sclerosis.

Biogen funded research study on BG-12 (Tecfidera), Protandim, SFN, tBHQ

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Repairing mechanisms 2
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Nrf2 activators: a novel strategy to promote oligodendrocyte survival in multiple sclerosis?

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Objectives:
To investigate the potential of different Nrf2 activators to boost antioxidant enzyme expression in oligodendrocytes and protect them from reactive oxygen species (ROS)-mediated cell death.

Background:
Oligodendrocyte damage and loss are key features of Multiple Sclerosis (MS) pathology and oligodendrocytes are particularly vulnerable to ROS-induced oxidative damage and cell death. Hence, a potential therapeutic strategy to protect these cells from ROS-mediated damage is urgently needed. To date, several compounds, including fumurate derivative BG-12, tert-Butylhydroquinone (tBHQ), sulforaphane (SFN) and protandim have potential anti-inflammatory and neuroprotective properties. These compounds are thought to exert their protective function via activation of the nuclear-factor-E2-related factor-2 (Nrf2) transcriptional pathway, which is involved in the production of antioxidant enzymes necessary for oxidative stress defense. We postulate that distinct Nrf2 activators boost antioxidant enzyme production in oligodendrocytes and limit ROS-mediated oligodendrocyte cell death.

Methods:
Primary rat oligodendrocytes and rat and human oligodendrocyte cell lines were treated with different concentrations of BG-12, tBHQ, SFN and protandim. Next, we analyzed the expression of Nrf2-mediated antioxidant enzymes by PCR and Western blot techniques. To study the beneficial effects of the different Nrf2 activators, we first incubated the oligodendrocytes with Nrf2 activators and subsequently exposed them to various concentrations of hydrogen peroxide and measured oligodendrocyte cell survival.

Results:
1. BG-12, tBHQ, SFN and protandim are well-tolerated and strongly induce Nrf2-driven antioxidant enzyme production in oligodendrocytes, with protandim showing the most potent induction.
2. Nrf2 activators are able to protect oligodendrocytes against ROS-induced cytotoxicity.
Conclusions: Our findings indicate that several Nrf2 activators are able to significantly increase antioxidant enzyme production in oligodendrocytes. Interestingly, protandim, a dietary supplement consisting of herbal ingredients, was the most potent inducer and therefore may be the most suited as a therapeutic strategy. Importantly, Nrf2-mediated antioxidant enzyme expression in oligodendrocytes resulted in enhanced oligodendrocyte survival during an oxidative attack.

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