

Preventive Role of Cannabinoids Derivate against Methylphenidate-Induced Oxidative Stress and Inflammation: The Hypothetical Function of Keap1/Nrf2/ARE Signaling and Proposal of a Treatment Strategy for Neurodegeneration

Hypothesis

Chronic methylphenidate abuse or administration causes oxidative stress, inflammation, and mitochondrial dysfunction in brain cells that require therapeutic approaches to inhibit neurotoxicity and neurodegeneration of these types.^[1,2] Nonetheless, the function of methylphenidate in the induction of neurodegeneration or neuroprotection is uncertain, but most of the data support the function of methylphenidate in neurodegeneration.^[3] As we know, Nrf2 (nuclear erythroid 2-related factor 2) is a basic region of leucine-zipper transcription factor that binds to the antioxidant response element (ARE) and thus regulates the expression of a large number of genes involved in cellular antioxidant and antiinflammatory defense as well as mitochondrial protection.^[4,5] Keap1 (Kelch ECH associating protein 1) is a repressor protein which binds to Nrf2 and promotes its degradation through the pathway of ubiquitin-proteasome.^[5,6] Nrf2/ARE signaling pathway is a key neuroprotection mediator.^[6] Oxidative stress, inflammation, and mitochondrial dysfunction have been identified as important mechanisms for methylphenidate-induced neurodegeneration.^[1,2] Despite the role of methylphenidate in the induction of neurodegeneration, a previous study has shown controversial data and reported that methylphenidate, by reducing proinflammatory microglia and increasing BDNF and Nrf2 mRNA levels, may increase cognitive deficits and depressive behaviors in myotonic type 1 disease in Mbnl2 knockout mice;^[7] however, the exact role of Keap1/Nrf2/ARE signaling pathway in methylphenidate-induced oxidative stress, inflammation, and mitochondrial dysfunction remains unclear. Neuroprotective approach to the prevention, treatment, or management of methylphenidate-induced oxidative stress, inflammation, and mitochondrial dysfunction through a novel neuroprotective agent is continuously superior to any other therapeutic strategy.^[8,9] The explanation, introduction, and development of a potent novel neuroprotective agent is therefore necessary.^[10,11] Studies have shown the possible neuroprotective and antiinflammatory efficacy of cannabinoid compounds and their derivatives such as cannabidiol (CBD) and delta 9 tetrahydrocannabinol against various neurodegenerative diseases and disorders over the past few years.^[9,12-14] According to some previous studies, cannabinoid derivative by direct activation of Nrf2/ARE or by inhibition of Keap1, a Nrf2 repressor protein, exerts

its antioxidant and antiinflammatory effects and also induces mitochondrial biogenesis, but the specific role of Nrf2/ARE in the neuroprotective function of cannabinoid compounds was not entirely understood.^[15,16] The function of Nrf2 signaling pathways in mediating the protective and beneficial effects of cannabinoids on cardiovascular, musculoskeletal, gastro-hepatic, and other systems was also demonstrated in many previous studies,^[17,18] but its clear role in brain function and the role of Nrf2 signaling pathways in the mediation of cannabinoid-derived neuroprotection remains unclear and seems to require further assessment. According to the aforementioned literature on the neurotoxicity properties of methylphenidate and cannabinoid neuroprotective effects, we may assume that the use of cannabinoids in methylphenidate-dependent subject will produce antioxidant and antiinflammatory effects and cause mitochondrial biogenesis and neuroprotection in methylphenidate-induced neural cell degeneration; also, based on the role of Nrf2/ARE signaling pathways in antioxidant and antiinflammatory processes, it appears that methylphenidate can cause neurodegeneration by activation of Keap1 or direct inhibition of the Nrf2/ARE pathway. Cannabinoid derived by direct activation of the Nof2/ARE signaling pathways or their repressor, Keap1, is also expected to be capable of managing the sequel to methylphenidate abuses such as oxidative stress, inflammation, and neurodegeneration, but this claim requires molecular assessment in both experimental and human studies [Figure 1].

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References

1. Motaghinejad M, Motevalian M, Shabab B. Effects of chronic treatment with methylphenidate on oxidative stress and

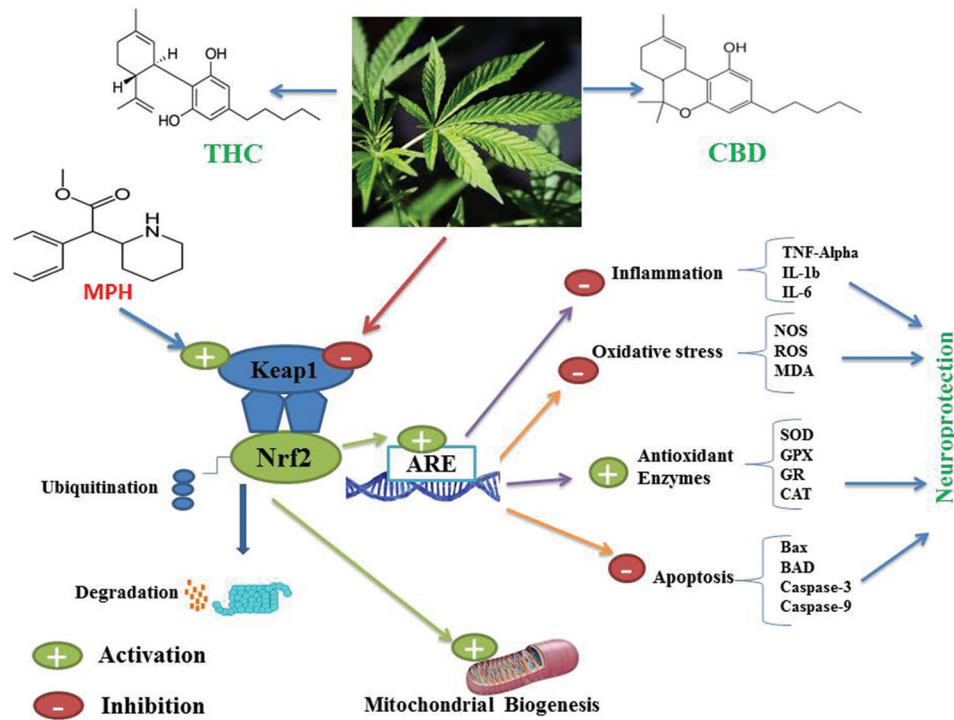


Figure 1: Possible inhibitory activity of cannabinoid derivatives such as cannabidiol (CBD) and delta 9 tetrahydrocannabinol (9 THC) against methylphenidate—oxidative stress, inflammation, apoptosis, and mitochondrial dysfunction. Methylphenidate has been suggested to induce oxidative stress, inflammation, apoptosis, and mitochondrial dysfunction through activation of Keap1 or direct inhibition of the Nrf2/ARE pathway. Cannabinoid derivative by direct activation of Nrf2/ARE signaling pathways or by inhibition of their repressor, Keap1, can control the sequel of methylphenidate abuse, such as oxidative stress, inflammation, and neurodegeneration, and can cause neuroprotection against methylphenidate-induced neurodegeneration. MPH: Methylphenidate, CBD: Cannabidiol, 9 THC: Delta 9 tetrahydrocannabinol, Nrf-2: Nuclear erythroid 2-related factor 2, Keap1: Kelch ECH associating protein 1, ARE: Antioxidant response element, TNF- α : Tumor necrosis factor, IL-6: Interleukin-6, IL-1 β : Interleukin-1 β , SOD: Superoxide dismutases, GPx: Glutathione peroxidase, GR: Glutathione reductase, CAT: Catalase

inflammation in hippocampus of adult rats. *Neurosci Lett* 2016;619:106-13.

- Coelho-Santos V, Cardoso FL, Leitão RA, Fontes-Ribeiro CA, Silva AP. Impact of developmental exposure to methylphenidate on rat brain's immune privilege and behavior: Control versus ADHD model. *Brain Behav Immun* 2018;68:169-82.
- Storebø OJ, Ramstad E, Krogh HB, Nilausen TD, Skoog M, Holmskov M, *et al.* Methylphenidate for children and adolescents with attention deficit hyperactivity disorder (ADHD). *Cochrane Database Syst Rev* 2015;CD009885. doi: 10.1002/14651858.CD009885.pub2.
- Tu W, Wang H, Li S, Liu Q, Sha H. The anti-inflammatory and anti-oxidant mechanisms of the Keap1/Nrf2/ARE signaling pathway in chronic diseases. *Aging Dis* 2019;10:637-51.
- Petri S, Körner S, Kiaei M. Nrf2/ARE signaling pathway: Key mediator in oxidative stress and potential therapeutic target in ALS. *Neurol Res Int* 2012;2012:878030.
- Zhang L, Yang J, Wu S, Jin C, Lu X, Hu X, *et al.* Activation of Nrf2/ARE signaling pathway attenuates lanthanum chloride induced injuries in primary rat astrocytes. *Metallomics* 2017;9:1120-31.
- Ramon-Duaso C, Gener T, Consegal M, Fernández-Avilés C, Gallego JJ, Castarlenas L, *et al.* Methylphenidate attenuates the cognitive and mood alterations observed in Mbnl2 knockout mice and reduces microglia overexpression. *Cereb Cortex* 2019;29:2978-97.
- Dang D-K, Shin E-J, Mai A-T, Jang C-G, Nah S-Y, Jeong JH, *et al.* Genetic or pharmacological depletion of cannabinoid CB1 receptor protects against dopaminergic neurotoxicity induced by methamphetamine in mice. *Free Radic Biol Med* 2017;108:204-224.
- Kendall DA, Yudowski GA. Cannabinoid receptors in the central nervous system: Their signaling and roles in disease. *Front Cell Neurosci* 2017;10:294.
- Motaghinejad M, Motevalian M, Fatima S, Hashemi H, Gholami M. Curcumin confers neuroprotection against alcohol-induced hippocampal neurodegeneration via CREB-BDNF pathway in rats. *Biomed Pharmacother* 2017;87:721-40.
- Liu Q-R, Canseco-Alba A, Zhang H-Y, Tagliaferro P, Chung M, Dennis E, *et al.* Cannabinoid type 2 receptors in dopamine neurons inhibits psychomotor behaviors, alters anxiety, depression and alcohol preference. *Sci Rep* 2017;7:17410.
- Campos AC, Fogaça MV, Sonogo AB, Guimarães FS. Cannabidiol, neuroprotection and neuropsychiatric disorders. *Pharmacol Res* 2016;112:119-27.
- Borges R, da Silva A. Cannabidiol as an antioxidant. *Handbook of Cannabis and Related Pathologies*. Elsevier; 2017. e122-30.
- Mori MA, Meyer E, Soares LM, Milani H, Guimarães FS, de Oliveira RMW. Cannabidiol reduces neuroinflammation and promotes neuroplasticity and functional recovery after brain ischemia. *Prog Neuropsychopharmacol Biol Psychiatry* 2017;75:94-105.
- Li X, Han D, Wang Y, Fan M, Li X, Cao F. GW27-e1152 activation of cannabinoid receptor II-CB2 ameliorates cardiac fibrosis after myocardial infarction via Nrf2-mediated inhibition

of TGF β -1/Smad3 pathway. *J Am Coll Cardiol* 2016;68:C42.

16. Casares L, García V, Garrido-Rodríguez M, Millán E, Collado JA, García-Martín A, *et al.* Cannabidiol induces antioxidant pathways in keratinocytes by targeting BACH1. *Redox Biol* 2020;28:101321.
17. Li X, Han D, Tian Z, Gao B, Fan M, Li C, *et al.* Activation of cannabinoid receptor type II by AM1241 ameliorates myocardial fibrosis via Nrf2-mediated inhibition of TGF- β 1/Smad3 pathway in myocardial infarction mice. *Cell Physiol Biochem* 2016;39:1521-36.
18. Zhang M, Zhang M, Wang L, Yu T, Jiang S, Jiang P, *et al.* Activation of cannabinoid type 2 receptor protects skeletal muscle from ischemia-reperfusion injury partly via Nrf2 signaling. *Life Sci* 2019;230:55-67.

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