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Metformin Therapy Attenuates Pro-inflammatory Microglia by Inhibiting NF-κB in Cuprizone Demyelinating Mouse Model of Multiple Sclerosis

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Abstract

Multiple sclerosis (MS) is a chronic disorder characterized by reactive gliosis, inflammation, and demyelination. Microglia plays a crucial role in the pathogenesis of MS and has the dynamic plasticity to polarize between pro-inflammatory (M1) and anti-inflammatory (M2) phenotypes. Metformin , a glucose-lowering drug, attenuates inflammatory responses by activating adenosine monophosphate protein kinase (AMPK) which suppresses nuclear factor kappa B (NF-κB). In this study, we indirectly investigated whether metformin therapy would regulate microglia activity in the cuprizone (CPZ)-induced demyelination mouse model of MS via measuring the markers associated with pro- and anti-inflammatory microglia . Evaluation of myelin by luxol fast blue staining revealed that metformin treatment (CPZ + Met) diminished demyelination, in comparison to CPZ mice . In addition, metformin therapy significantly alleviated reactive microgliosis and astrogliosis in the corpus callosum, as measured by Iba-1 and GFAP staining. Moreover, metformin treatment significantly downregulated the expression of pro-inflammatory associated genes (iNOS, H2-Aa, and TNF-α) in the corpus callosum, whereas expression of anti-inflammatory markers (Arg1, Mrc1, and IL10) was not promoted, compared to CPZ mice . Furthermore, protein levels of iNOS (pro-inflammatory marker) were significantly decreased in the metformin group, while those of Trem2 (anti-inflammatory marker) were increased. In addition, metformin significantly increased AMPK activation in CPZ mice . Finally, metformin administration significantly reduced the activation level of NF-κB in CPZ mice . In summary, our data revealed that metformin attenuated pro-inflammatory microglia markers through suppressing NF-κB activity. The positive effects of metformin on microglia and remyelination suggest that it could be used as a promising candidate to lessen the incidence of inflammatory neurodegenerative diseases such as MS. © 2021, The Author(s), under exclusive licence to Springer Science+Business Media, LLC, part of Springer Nature.

Author keywords

Cuprizone ; Metformin ; Microglia activity; Multiple sclerosis ; Neuroinflammation; NF-κB

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References (91)

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1 Adilijiang, A., Guan, T., He, J., Hartle, K., Wang, W., Li, X.

The protective effects of areca catechu extract on cognition and social interaction deficits in a cuprizone-induced demyelination model (Open Access)

(2015) *Evidence-based Complementary and Alternative Medicine*, 2015, art. no. 426092. Cited 20 times.
http://www.hindawi.com/journals/ecam/contents.html
doi: 10.1155/2015/426092

View at Publisher

2 Algire, C., Moiseeva, O., Deschênes-Simard, X., Amrein, L., Petruccelli, L., Birman, E., Viollet, B., (...), Pollak, M.N.

Metformin reduces endogenous reactive oxygen species and associated DNA damage

(2012) *Cancer Prevention Research*, 5 (4), pp. 536-543. Cited 216 times.
http://cancerpreventionresearch.aacrjournals.org/content/5/4/536.full.pdf+html
doi: 10.1158/1940-6207.CAPR-11-0536

View at Publisher

3 Amende, I., Kale, A., McCue, S., Glazier, S., Morgan, J.P., Hampton, T.G.

Gait dynamics in mouse models of Parkinson's disease and Huntington's disease (Open Access)

(2005) *Journal of NeuroEngineering and Rehabilitation*, 2. Cited 110 times.
http://www.jneuroengrehab.com/content/pdf/1743-0003-2-20.pdf
doi: 10.1186/1743-0003-2-20

View at Publisher

4 Arnoux, I., Willam, M., Griesche, N., Krummeich, J., Watari, H., Offermann, N., Weber, S., (...), Stroh, A.

Metformin reverses early cortical network dysfunction and behavior changes in Huntington's disease (Open Access)

(2018) *eLife*, 7, art. no. e38744. Cited 31 times.
https://elifesciences.org/download/aHR0cHM6Ly9jZG4uZWxpZmVzY2llbmNlcy5vcmcvYXJ0aWNsZXMvMzg3NDQvZWxpZmUtMzg3NDQtdjMucGRm/elife-38744-v3.pdf?_hash=bjkDMnsO%2BwBP5pupWE6p0%2F2SrPm6wQ0VsVRcff5uaSs%3D
doi: 10.7554/eLife.38744

View at Publisher

5 Aryanpour, R., Pasbakhsh, P., Zibara, K., Namjoo, Z., Beigi Boroujeni, F., Shahbeigi, S., Kashani, I.R., (...), Zendehdel, A.

Progesterone therapy induces an M1 to M2 switch in microglia phenotype and suppresses NLRP3 inflammasome in a cuprizone-induced demyelination mouse model

(2017) *International Immunopharmacology*, 51, pp. 131-139. Cited 65 times.
www.elsevier.com/locate/intimp
doi: 10.1016/j.intimp.2017.08.007

View at Publisher

6 Aryanpour, R., Pasbakhsh, P., Zibara, K., Namjoo, Z., Beigi Boroujeni, F., Shahbeigi, S., Kashani, I.R., (...), Zendehdel, A.

Progesterone therapy induces an M1 to M2 switch in microglia phenotype and suppresses NLRP3 inflammasome in a cuprizone-induced demyelination mouse model

(2017) *International Immunopharmacology*, 51, pp. 131-139. Cited 65 times.
www.elsevier.com/locate/intimp
doi: 10.1016/j.intimp.2017.08.007

View at Publisher

7 Aryanpour, R., Zibara, K., Pasbakhsh, P., Jame'ei, S.B., Namjoo, Z., Ghanbari, A., Mahmoudi, R., (...), Kashani, I.R.

17β-Estradiol Reduces Demyelination in Cuprizone-fed Mice by Promoting M2 Microglia Polarity and Regulating NLRP3 Inflammasome

(2021) *Neuroscience*, 463, pp. 116-127.
www.elsevier.com/locate/neuroscience
doi: 10.1016/j.neuroscience.2021.03.025

View at Publisher

8 Barati, S., Ragerdi Kashani, I., Moradi, F., Tahmasebi, F., Mehrabi, S., Barati, M., Joghataei, M.T.

Mesenchymal stem cell mediated effects on microglial phenotype in cuprizone-induced demyelination model

(2019) *Journal of Cellular Biochemistry*, 120 (8), pp. 13952-13964. Cited 15 times.
http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1097-4644
doi: 10.1002/jcb.28670

View at Publisher

9 Bernardes, D., Oliveira, A.L.R.

Comprehensive catwalk gait analysis in a chronic model of multiple sclerosis subjected to treadmill exercise training (Open Access)

(2017) *BMC Neurology*, 17 (1), art. no. 160. Cited 14 times.
http://www.biomedcentral.com/bmcneurol/
doi: 10.1186/s12883-017-0941-z

View at Publisher

10 Bonetti, B., Stegagno, C., Moretto, G., Rizzuto, N., Cannella, B., Raine, C.
Localization of NFkB in multiple sclerosis lesions: implications for oligodendrocyte damage
(1998) *J Neuroimmunol*, 90 (1), p. 71.

11 Brousse, B., Mercier, O., Magalon, K., Daian, F., Durbec, P., Cayre, M.

Endogenous neural stem cells modulate microglia and protect against demyelination (Open Access)

(2021) *Stem Cell Reports*, 16 (7), pp. 1792-1804.
http://www.elsevier.com/journals/stem-cell-reports/2213-6711
doi: 10.1016/j.stemcr.2021.05.002

View at Publisher

12 Brück, W., Pförtner, R., Pham, T., Zhang, J., Hayardeny, L., Piryatinsky, V., Hanisch, U.-K., (...), Wegner, C.

Reduced astrocytic NF-κB activation by laquinimod protects from cuprizone-induced demyelination (Open Access)

(2012) *Acta Neuropathologica*, 124 (3), pp. 411-424. Cited 125 times.
doi: 10.1007/s00401-012-1009-1

View at Publisher

13 Cai, Z., Hussain, M.D., Yan, L.-J.

Microglia, neuroinflammation, and beta-amyloid protein in Alzheimer's disease

(2014) *International Journal of Neuroscience*, 124 (5), pp. 307-321. Cited 262 times.
www.tandf.co.uk/journals/titles/00207454.asp
doi: 10.3109/00207454.2013.833510

View at Publisher

14 Cantoni, C., Bollman, B., Licastro, D., Xie, M., Mikesell, R., Schmidt, R., Yuede, C.M., (...), Piccio, L.

TREM2 regulates microglial cell activation in response to demyelination in vivo (Open Access)

(2015) *Acta Neuropathologica*, 129 (3), pp. 429-447. Cited 123 times.
link.springer.de/link/service/journals/00401/index.htm
doi: 10.1007/s00401-015-1388-1

View at Publisher

15 Cherry, J.D., Olschowka, J.A., O'Banion, M.K.

Neuroinflammation and M2 microglia: The good, the bad, and the inflamed (Open Access)

(2014) *Journal of Neuroinflammation*, 11, art. no. 98. Cited 827 times.
http://www.jneuroinflammation.com/content/11/1/98
doi: 10.1186/1742-2094-11-98

View at Publisher

16 Chu, F., Shi, M., Zheng, C., Shen, D., Zhu, J., Zheng, X., Cui, L.

The roles of macrophages and microglia in multiple sclerosis and experimental autoimmune encephalomyelitis

(2018) *Journal of Neuroimmunology*, 318, pp. 1-7. Cited 109 times.
www.elsevier.com/locate/jneuroim
doi: 10.1016/j.jneuroim.2018.02.015

View at Publisher

17 Cignarella, F., Filipello, F., Bollman, B., Cantoni, C., Locca, A., Mikesell, R., Manis, M., (...), Piccio, L.

TREM2 activation on microglia promotes myelin debris clearance and remyelination in a model of multiple sclerosis (Open Access)

(2020) *Acta Neuropathologica*, 140 (4), pp. 513-534. Cited 31 times.
link.springer.de/link/service/journals/00401/index.htm
doi: 10.1007/s00401-020-02193-z

View at Publisher

18 Citraro, R., Leo, A., Constanti, A., Russo, E., De Sarro, G.

MTOR pathway inhibition as a new therapeutic strategy in epilepsy and epileptogenesis (Open Access)

(2016) *Pharmacological Research*, 107, pp. 333-343. Cited 106 times.
http://www.elsevier.com/inca/publications/store/6/2/2/9/3/1/index.htt
doi: 10.1016/j.phrs.2016.03.039

View at Publisher

19 Dendrou, C.A., Fugger, L., Friese, M.A.

Immunopathology of multiple sclerosis

(2015) *Nature Reviews Immunology*, 15 (9), pp. 545-558. Cited 981 times.
http://www.nature.com/nri/index.html
doi: 10.1038/nri3871

View at Publisher

20 Devanney, N.A., Stewart, A.N., Gensel, J.C.

Microglia and macrophage metabolism in CNS injury and disease: The role of immunometabolism in neurodegeneration and neurotrauma (Open Access)

(2020) *Experimental Neurology*, 329, art. no. 113310. Cited 36 times.
http://www.elsevier.com/inca/publications/store/6/2/2/8/2/8/index.htt
doi: 10.1016/j.expneurol.2020.113310

View at Publisher

21 Elbaz, E.M., Senousy, M.A., El-Tanbouly, D.M., Sayed, R.H.

Neuroprotective effect of linagliptin against cuprizone-induced demyelination and behavioural dysfunction in mice: A pivotal role of AMPK/SIRT1 and JAK2/STAT3/NF-κB signalling pathway modulation

(2018) *Toxicology and Applied Pharmacology*, 352, pp. 153-161. Cited 33 times.
http://www.elsevier.com/inca/publications/store/6/2/2/9/5/1/index.htt
doi: 10.1016/j.taap.2018.05.035

View at Publisher

22 Elbaz, E.M., Senousy, M.A., El-Tanbouly, D.M., Sayed, R.H.

Neuroprotective effect of linagliptin against cuprizone-induced demyelination and behavioural dysfunction in mice: A pivotal role of AMPK/SIRT1 and JAK2/STAT3/NF-κB signalling pathway modulation

(2018) *Toxicology and Applied Pharmacology*, 352, pp. 153-161. Cited 33 times.
http://www.elsevier.com/inca/publications/store/6/2/2/9/5/1/index.htt
doi: 10.1016/j.taap.2018.05.035

View at Publisher

23 Goldberg, J., Clarner, T., Beyer, C., Kipp, M.

Anatomical Distribution of Cuprizone-Induced Lesions in C57BL6 Mice

(2015) *Journal of Molecular Neuroscience*, 57 (2), pp. 166-175. Cited 49 times.
http://www.springer.com/humana+press/journal/12031
doi: 10.1007/s12031-015-0595-5

View at Publisher

24 Groebe, A., Clarner, T., Baumgartner, W., Dang, J., Beyer, C., Kipp, M.

Cuprizone treatment induces distinct demyelination, astrocytosis, and microglia cell invasion or proliferation in the mouse cerebellum

(2009) *Cerebellum*, 8 (3), pp. 163-174. Cited 82 times.
doi: 10.1007/s12311-009-0099-3

View at Publisher

25 Gudi, V., Gingele, S., Skripuletz, T., Stangel, M.

Glial response during cuprizone-induced de- and remyelination in the CNS: Lessons learned (Open Access)

(2014) *Frontiers in Cellular Neuroscience*, 8 (MAR), art. no. 73. Cited 183 times.
http://journal.frontiersin.org/Journal/10.3389/fncel.2014.00073/pdf
doi: 10.3389/fncel.2014.00073

View at Publisher

26 Guerrero, B.L., Sicotte, N.L.

Microglia in Multiple Sclerosis: Friend or Foe? (Open Access)

(2020) *Frontiers in Immunology*, 11, art. no. 374. Cited 32 times.
https://www.frontiersin.org/journals/immunology#
doi: 10.3389/fimmu.2020.00374

View at Publisher

27 Gveric, D., Kaltschmidt, C., Cuzner, M.L., Newcombe, J.

Transcription factor NF-κB and inhibitor IκBα are localized in macrophages in active multiple sclerosis lesions (Open Access)

(1998) *Journal of Neuropathology and Experimental Neurology*, 57 (2), pp. 168-178. Cited 94 times.
http://journals.lww.com/jneuropath
doi: 10.1097/00005072-199802000-00008

View at Publisher

28 Hattori, Y., Suzuki, K., Hattori, S., Kasai, K.

Metformin inhibits cytokine-induced nuclear factor κB activation via AMP-activated protein kinase activation in vascular endothelial cells (Open Access)

(2006) *Hypertension*, 47 (6), pp. 1183-1188. Cited 343 times.
doi: 10.1161/01.HYP.0000221429.94591.72

View at Publisher

29 Houshmand, F., Barati, M., Golab, F., Ramezani-sefidar, S., Tanbakooie, S., Tabatabaei, M., Amiri, M., (...), Sanadgol, N.

Metformin-induced AMPK activation stimulates remyelination through induction of neurotrophic factors, downregulation of NogoA and recruitment of Olig2+ precursor cells in the cuprizone murine model of multiple sclerosis (Open Access)

(2019) *DARU, Journal of Pharmaceutical Sciences*, 27 (2), pp. 583-592. Cited 8 times.
https://rd.springer.com/journal/40199
doi: 10.1007/s40199-019-00286-z

View at Publisher

30 Houshmand, F., Barati, M., Golab, F., Ramezani-sefidar, S., Tanbakooie, S., Tabatabaei, M., Amiri, M., (...), Sanadgol, N.

Metformin-induced AMPK activation stimulates remyelination through induction of neurotrophic factors, downregulation of NogoA and recruitment of Olig2+ precursor cells in the cuprizone murine model of multiple sclerosis (Open Access)

(2019) *DARU, Journal of Pharmaceutical Sciences*, 27 (2), pp. 583-592. Cited 8 times.
https://rd.springer.com/journal/40199
doi: 10.1007/s40199-019-00286-z

View at Publisher

31 Hwang, I.K., Kim, I.Y., Joo, E.J., Shin, J.H., Choi, J.W., Won, M.-H., Yoon, Y.S., (...), Seong, J.K.

Metformin normalizes type 2 diabetes-induced decrease in cell proliferation and neuroblast differentiation in the rat dentate gyrus

(2010) *Neurochemical Research*, 35 (4), pp. 645-650. Cited 29 times.
doi: 10.1007/s11064-009-0115-5

View at Publisher

32 Iaccarino, H.F., Singer, A.C., Martorell, A.J., Rudenko, A., Gao, F., Gillingham, T.Z., Mathys, H., (...), Tsai, L.-H.

Gamma frequency entrainment attenuates amyloid load and modifies microglia (Open Access)

(2016) *Nature*, 540 (7632), pp. 230-235. Cited 395 times.
http://www.nature.com/nature/index.html
doi: 10.1038/nature20587

View at Publisher

33 Jeon, S.-M.

Regulation and function of AMPK in physiology and diseases (Open Access)

(2016) *Experimental & molecular medicine*, 48 (7), p. e245. Cited 422 times.
doi: 10.1038/emm.2016.81

View at Publisher

34 Jha, M.K., Lee, W.-H., Suk, K.

Functional polarization of neuroglia: Implications in neuroinflammation and neurological disorders

(2016) *Biochemical Pharmacology*, 103, pp. 1-16. Cited 131 times.
www.elsevier.com/locate/biochempharm
doi: 10.1016/j.bcp.2015.11.003

View at Publisher

35 Jin, Q., Cheng, J., Liu, Y., Wu, J., Wang, X., Wei, S., Zhou, X., (...), Zhen, X.

Improvement of functional recovery by chronic metformin treatment is associated with enhanced alternative activation of microglia/macrophages and increased angiogenesis and neurogenesis following experimental stroke

(2014) *Brain, Behavior, and Immunity*, 40, pp. 131-142. Cited 173 times.
http://www.elsevier.com/inca/publications/store/6/2/2/8/0/0/index.htt
doi: 10.1016/j.bbi.2014.03.003

View at Publisher

36 Jing, Y., Wu, F., Li, D., Yang, L., Li, Q., Li, R.

Metformin improves obesity-associated inflammation by altering macrophages polarization

(2018) *Molecular and Cellular Endocrinology*, 461, pp. 256-264. Cited 84 times.
www.elsevier.com/locate/mce
doi: 10.1016/j.mce.2017.09.025

View at Publisher

37 Kheirandish, M., Mahboobi, H., Yazdanparast, M., Kamal, W., Kamal, M.A.

Anti-cancer effects of metformin: Recent evidences for its role in prevention and treatment of cancer

(2018) *Current Drug Metabolism*, 19 (9), pp. 793-797. Cited 36 times.
http://www.eurekaselect.com/161323
doi: 10.2174/1389200219666180416161846

View at Publisher

38 Kim, J., Kundu, M., Viollet, B., Guan, K.L.

AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1 (Open Access)

(2011) *Nature Cell Biology*, 13 (2), pp. 132-141. Cited 3804 times.
doi: 10.1038/ncb2152

View at Publisher

39 Kim, J., Yang, G., Kim, Y., Kim, J., Ha, J.

AMPK activators: Mechanisms of action and physiological activities (Open Access)

(2016) *Experimental and Molecular Medicine*, 48 (4), art. no. e224. Cited 295 times.
http://www.nature.com/press_releases/emm-relaunch.html
doi: 10.1038/emm.2016.16

View at Publisher

40 Kim, W., Hahn, K.R., Jung, H.Y., Kwon, H.J., Nam, S.M., Kim, J.W., Park, J.H., (...), Hwang, I.K.

Melatonin ameliorates cuprizone-induced reduction of hippocampal neurogenesis, brain-derived neurotrophic factor, and phosphorylation of cyclic AMP response element-binding protein in the mouse dentate gyrus (Open Access)

(2019) *Brain and Behavior*, 9 (9), art. no. e01388. Cited 14 times.
http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2157-9032
doi: 10.1002/brb3.1388

View at Publisher

41 Kipp, M., Clarner, T., Dang, J., Copray, S., Beyer, C.

The cuprizone animal model: New insights into an old story

(2009) *Acta Neuropathologica*, 118 (6), pp. 723-736. Cited 309 times.
doi: 10.1007/s00401-009-0591-3

View at Publisher

42 Kiriyama, Y., Nochi, H.

The function of autophagy in neurodegenerative diseases (Open Access)

(2015) *International Journal of Molecular Sciences*, 16 (11), pp. 26797-26812. Cited 99 times.
http://www.mdpi.com/1422-0067/16/11/25990/pdf
doi: 10.3390/ijms161125990

View at Publisher

43 Kosaraju, J., Seegobin, M., Gouveia, A., Syal, C., Sarma, S.N., Lu, K.J., Ilin, J., (...), Wang, J.

Metformin promotes CNS remyelination and improves social interaction following focal demyelination through CBP Ser436 phosphorylation

(2020) *Experimental Neurology*, 334, art. no. 113454.
http://www.elsevier.com/inca/publications/store/6/2/2/8/2/8/index.htt
doi: 10.1016/j.expneurol.2020.113454

View at Publisher

44 Largani, S.H.H., Borhani-Haghighi, M., Pasbakhsh, P., Mahabadi, V.P., Nekoonam, S., Shiri, E., Kashani, I.R., (...), Zendehdel, A.

Oligoprotective effect of metformin through the AMPK-dependent on restoration of mitochondrial hemostasis in the cuprizone-induced multiple sclerosis model

(2019) *Journal of Molecular Histology*, 50 (3), pp. 263-271. Cited 11 times.
http://www.kluweronline.com/issn/1567-2379/
doi: 10.1007/s10735-019-09824-0

View at Publisher

45 Lassmann, H.

Multiple sclerosis pathology (Open Access)

(2018) *Cold Spring Harbor Perspectives in Medicine*, 8 (3), art. no. a028936. Cited 183 times.
http://perspectivesinmedicine.cshlp.org/content/8/3/a028936.full.pdf
doi: 10.1101/cshperspect.a028936

View at Publisher

46 Lassmann, H., Van Horssen, J., Mahad, D.

Progressive multiple sclerosis: Pathology and pathogenesis

(2012) *Nature Reviews Neurology*, 8 (11), pp. 647-656. Cited 556 times.
http://www.nature.com/nrneurol/archive/index.html
doi: 10.1038/nrneurol.2012.168

View at Publisher

47 Legro, R.S., Barnhart, H.X., Schlaff, W.D., Carr, B.R., Diamond, M.P., Carson, S.A., Steinkampf, M.P., (...), Myers, E.R.

Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome (Open Access)

(2007) *New England Journal of Medicine*, 356 (6), pp. 551-566. Cited 736 times.
http://content.nejm.org/cgi/reprint/356/6/551.pdf
doi: 10.1056/NEJMoa063971

View at Publisher

48 Li, J., Deng, J., Sheng, W., Zuo, Z.

Metformin attenuates Alzheimer's disease-like neuropathology in obese, leptin-resistant mice (Open Access)

(2012) *Pharmacology Biochemistry and Behavior*, 101 (4), pp. 564-574. Cited 168 times.
doi: 10.1016/j.pbb.2012.03.002

View at Publisher

49 Lu, M., Su, C., Qiao, C., Bian, Y., Ding, J., Hu, G.

Metformin prevents dopaminergic neuron death in MPTP/P-induced mouse model of Parkinson's disease via autophagy and mitochondrial ROS clearance (Open Access)

(2016) *International Journal of Neuropsychopharmacology*, 19 (9), pp. 1-11. Cited 117 times.
http://ijnp.oxfordjournals.org/
doi: 10.1093/ijnp/pyw047

View at Publisher

50 Luo, C., Jian, C., Liao, Y., Huang, Q., Wu, Y., Liu, X., Zou, D., (...), Wu, Y.

The role of microglia in multiple sclerosis (Open Access)

(2017) *Neuropsychiatric Disease and Treatment*, 13, pp. 1661-1667. Cited 74 times.
https://www.dovepress.com/getfile.php?fileID=37107
doi: 10.2147/NDT.S140634

View at Publisher

51 Manwani, B., Mccullough, L.D.

Function of the master energy regulator adenosine monophosphate-activated protein kinase in stroke (Open Access)

(2013) *Journal of Neuroscience Research*, 91 (8), pp. 1018-1029. Cited 54 times.
doi: 10.1002/jnr.23207

View at Publisher

52 Mc Guire, C., Prinz, M., Beyaert, R., van Loo, G.

Nuclear factor kappa B (NF-κB) in multiple sclerosis pathology

(2013) *Trends in Molecular Medicine*, 19 (10), pp. 604-613. Cited 88 times.
doi: 10.1016/j.molmed.2013.08.001

View at Publisher

53 Memmott, R.M., Mercado, J.R., Maier, C.R., Kawabata, S., Fox, S.D., Dennis, P.A.

Metformin prevents tobacco carcinogen-induced lung tumorigenesis (Open Access)

(2010) *Cancer Prevention Research*, 3 (9), pp. 1066-1076. Cited 323 times.
http://cancerpreventionresearch.aacrjournals.org/content/3/9/1066.full.pdf+html
doi: 10.1158/1940-6207.CAPR-10-0055

View at Publisher

54 Nakagawa, Y., Chiba, K.

Diversity and plasticity of microglial cells in psychiatric and neurological disorders

(2015) *Pharmacology and Therapeutics*, 154, pp. 21-35. Cited 86 times.
www.elsevier.com/locate/pharmthera
doi: 10.1016/j.pharmthera.2015.06.010

View at Publisher

55 Nakatake, R., Iida, H., Ishizaki, M., Matsui, K., Nakamura, Y., Kaibori, M., Nishizawa, M., (...), Okumura, T.

Metformin inhibits expression of the proinflammatory biomarker inducible nitric oxide synthase in hepatocytes (Open Access)

(2018) *Functional Foods in Health and Disease*, 8 (3), pp. 175-192. Cited 5 times.
https://ffhdj.com/index.php/ffhd/article/view/423
doi: 10.31989/ffhd.v8i3.423

View at Publisher

56 Nath, N., Khan, M., Paintlia, M.K., Hoda, Md.N., Giri, S.

Metformin attenuated the autoimmune disease of the central nervous system in animal models of multiple sclerosis (Open Access)

(2009) *Journal of Immunology*, 182 (12), pp. 8005-8014. Cited 236 times.
http://www.jimmunol.org/cgi/reprint/182/12/8005
doi: 10.4049/jimmunol.0803563

View at Publisher

57 Nath, N., Khan, M., Paintlia, M.K., Hoda, Md.N., Giri, S.

Metformin attenuated the autoimmune disease of the central nervous system in animal models of multiple sclerosis (Open Access)

(2009) *Journal of Immunology*, 182 (12), pp. 8005-8014. Cited 236 times.
http://www.jimmunol.org/cgi/reprint/182/12/8005
doi: 10.4049/jimmunol.0803563

View at Publisher

58 Nath, N., Khan, M., Rattan, R., Mangalam, A., Makkar, R.S., Meester, C.d., Bertrand, L., (...), Giri, S.

Loss of AMPK exacerbates experimental autoimmune encephalomyelitis disease severity (Open Access)

(2009) *Biochemical and Biophysical Research Communications*, 386 (1), pp. 16-20. Cited 55 times.
doi: 10.1016/j.bbrc.2009.05.106

View at Publisher

59 Negrotto, L., Farez, M.F., Correale, J.

Immunologic effects of metformin and pioglitazone treatment on metabolic syndrome and multiple sclerosis (Open Access)

(2016) *JAMA Neurology*, 73 (5), pp. 520-528. Cited 80 times.
http://archneur.jamanetwork.com/data/Journals/NEUR/935258/noi150104.pdf
doi: 10.1001/jamaneurol.2015.4807

View at Publisher

60 Neumann, H., Takahashi, K.

Essential role of the microglial triggering receptor expressed on myeloid cells-2 (TREM2) for central nervous tissue immune homeostasis

(2007) *Journal of Neuroimmunology*, 184 (1-2), pp. 92-99. Cited 183 times.
doi: 10.1016/j.jneuroim.2006.11.032

View at Publisher

61 Nyamoya, S., Leopold, P., Becker, B., Beyer, C., Hustadt, F., Schmitz, C., Michel, A., (...), Kipp, M.

G-Protein-Coupled Receptor Gpr17 Expression in Two Multiple Sclerosis Remyelination Models

(2019) *Molecular Neurobiology*, 56 (2), pp. 1109-1123. Cited 15 times.
http://www.springer.com/biomed/neuroscience/journal/12035
doi: 10.1007/s12035-018-1146-1

View at Publisher

62 Orihuela, R., McPherson, C.A., Harry, G.J.

Microglial M1/M2 polarization and metabolic states (Open Access)

(2016) *British Journal of Pharmacology*, 173 (4), pp. 649-665. Cited 630 times.
http://onlinelibrary.wiley.com/journal/10.1111/%28ISSN%291476-5381
doi: 10.1111/bph.13139

View at Publisher

63 Paintlia, A.S., Paintlia, M.K., Mohan, S., Singh, A.K., Singh, I.

AMP-activated protein kinase signaling protects oligodendrocytes that restore central nervous system functions in an experimental autoimmune encephalomyelitis model (Open Access)

(2013) *American Journal of Pathology*, 183 (2), pp. 526-541. Cited 36 times.
doi: 10.1016/j.ajpath.2013.04.030

View at Publisher

64 Peixoto, C.A., Oliveira, W.H.D., Araújo, S.M.D.R., Nunes, A.K.S.

AMPK activation: Role in the signaling pathways of neuroinflammation and neurodegeneration

(2017) *Experimental Neurology*, Part A 298, pp. 31-41. Cited 75 times.
http://www.elsevier.com/inca/publications/store/6/2/2/8/2/8/index.htt
doi: 10.1016/j.expneurol.2017.08.013

View at Publisher

65 Pott, F., Gingele, S., Clarner, T., Dang, J., Baumgartner, W., Beyer, C., Kipp, M.

Cuprizone effect on myelination, astrogliosis and microglia attraction in the mouse basal ganglia

(2009) *Brain Research*, 1305, pp. 137-149. Cited 60 times.
www.elsevier.com/locate/bri
doi: 10.1016/j.brainres.2009.09.084

View at Publisher

66 Praet, J., Guglielmetti, C., Berneman, Z., Van der Linden, A., Ponsaerts, P.

Cellular and molecular neuropathology of the cuprizone mouse model: Clinical relevance for multiple sclerosis (Open Access)

(2014) *Neuroscience and Biobehavioral Reviews*, 47, pp. 485-505. Cited 203 times.
www.elsevier.com/locate/neubiorev
doi: 10.1016/j.neubiorev.2014.10.004

View at Publisher

67 Qing, L., Fu, J., Wu, P., Zhou, Z., Yu, F., Tang, J.

Metformin induces the m2 macrophage polarization to accelerate the wound healing via regulating ampk/ mtor/nlrp3 inflammasome singling pathway

(2019) *American Journal of Translational Research*, 11 (2), art. no. AJTR0085206, pp. 655-668. Cited 55 times.
http://www.ajtr.org/files/ajtr0085206.pdf

68 Saijo, K., Glass, C.K.

Microglial cell origin and phenotypes in health and disease

(2011) *Nature Reviews Immunology*, 11 (11), pp. 775-787. Cited 675 times.
doi: 10.1038/nri3086

View at Publisher

69 Salminen, A., Hyttinen, J.M.T., Kaarniranta, K.

AMP-activated protein kinase inhibits NF-κB signaling and inflammation: Impact on healthspan and lifespan (Open Access)

(2011) *Journal of Molecular Medicine*, 89 (7), pp. 667-676. Cited 509 times.
doi: 10.1007/s00109-011-0748-0

View at Publisher

70 Sanadgol, N., Barati, M., Houshmand, F., Hassani, S., Clarner, T., shahlaei, M., Golab, F.

Metformin accelerates myelin recovery and ameliorates behavioral deficits in the animal model of multiple sclerosis via adjustment of AMPK/Nrf2/mTOR signaling and maintenance of endogenous oligodendrogenesis during brain self-repairing period

(2020) *Pharmacological Reports*, 72 (3), pp. 641-658. Cited 7 times.
https://link.springer.com/journal/43440
doi: 10.1007/s43440-019-00019-8

View at Publisher

71 Sanadgol, N., Barati, M., Houshmand, F., Hassani, S., Clarner, T., shahlaei, M., Golab, F.

Metformin accelerates myelin recovery and ameliorates behavioral deficits in the animal model of multiple sclerosis via adjustment of AMPK/Nrf2/mTOR signaling and maintenance of endogenous oligodendrogenesis during brain self-repairing period

(2020) *Pharmacological Reports*, 72 (3), pp. 641-658. Cited 7 times.
https://link.springer.com/journal/43440
doi: 10.1007/s43440-019-00019-8

View at Publisher

72 Sanadgol, N., Golab, F., Mostafaie, A., Mehdizadeh, M., Khalseh, R., Mahmoudi, M., Abdollahi, M., (...), Sharifzadeh, M.

Low, but not high, dose triptolide controls neuroinflammation and improves behavioral deficits in toxic model of multiple sclerosis by dampening of NF-κB activation and acceleration of intrinsic myelin repair

(2018) *Toxicology and Applied Pharmacology*, 342, pp. 86-98. Cited 17 times.
http://www.elsevier.com/inca/publications/store/6/2/2/9/5/1/index.htt
doi: 10.1016/j.taap.2018.01.023

View at Publisher

73 Sanchez-Guajardo, V., Tentillier, N., Romero-Ramos, M.

The relation between α-synuclein and microglia in Parkinson's disease: Recent developments

(2015) *Neuroscience*, 302, pp. 47-58. Cited 104 times.
www.elsevier.com/locate/neuroscience
doi: 10.1016/j.neuroscience.2015.02.008

View at Publisher

74 Srinivasan, M., Lahiri, D.K.

Significance of NF-κB as a pivotal therapeutic target in the neurodegenerative pathologies of Alzheimer's disease and multiple sclerosis (Open Access)

(2015) *Expert Opinion on Therapeutic Targets*, 19 (4), pp. 471-487. Cited 95 times.
doi: 10.1517/14728222.2014.989834

View at Publisher

75 Sun, J., Huang, N., Ma, W., Zhou, H., Lai, K.

Protective effects of metformin on lipopolysaccharide-induced airway epithelial cell injury via NF-κB signaling inhibition (Open Access)

(2019) *Molecular Medicine Reports*, 19 (3), pp. 1817-1823. Cited 14 times.
https://www.spandidos-publications.com/mmr/19/3/1809/download
doi: 10.3892/mmr.2019.9807

View at Publisher

76 Sun, Y., Tian, T., Gao, J., Liu, X., Hou, H., Cao, R., Li, B., (...), Guo, L.

Metformin ameliorates the development of experimental autoimmune encephalomyelitis by regulating T helper 17 and regulatory T cells in mice

(2016) *Journal of Neuroimmunology*, 292, pp. 58-67. Cited 64 times.
www.elsevier.com/locate/jneuroim
doi: 10.1016/j.jneuroim.2016.01.014

View at Publisher

77 Tang, Y., Le, W.

Differential Roles of M1 and M2 Microglia in Neurodegenerative Diseases

(2016) *Molecular Neurobiology*, 53 (2), pp. 1181-1194. Cited 779 times.
http://www.springer.com/biomed/neuroscience/journal/12035
doi: 10.1007/s12035-014-9070-5

View at Publisher

78 Tayara, K., Espinosa-Oliva, A.M., García-Domínguez, I., Ismaiel, A.A., Boza-Serrano, A., Deierborg, T., Machado, A., (...), de Pablos, R.M.

Divergent effects of metformin on an inflammatory model of Parkinson's disease (Open Access)

(2018) *Frontiers in Cellular Neuroscience*, 12, art. no. 440. Cited 12 times.
https://www.frontiersin.org/articles/10.3389/fncel.2018.00440/pdf
doi: 10.3389/fncel.2018.00440

View at Publisher

79 Torkildsen, Ø., Brunborg, L.A., Myhr, K.-M., Bø, L.

The cuprizone model for demyelination

(2008) *Acta Neurologica Scandinavica*, 117 (SUPPL. 188), pp. 72-76. Cited 170 times.
doi: 10.1111/j.1600-0404.2008.01036.x

View at Publisher

80 Vega-Riquer, J.M., Mendez-Victoriano, G., Morales-Luckie, R.A., Gonzalez-Perez, O.

Five decades of cuprizone, an updated model to replicate demyelinating diseases (Open Access)

(2019) *Current Neuropharmacology*, 17 (2), pp. 129-141. Cited 45 times.
http://www.eurekaselect.com/node/154244
doi: 10.2174/1570159X15666170717120343

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