Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

MANF

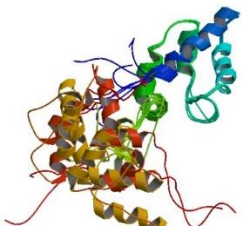
Evidence Summary

Neurotrophic factor with anti-inflammatory and antioxidant activity. May protect cells against age-related damage by protecting against ER stress. Not yet tested as a therapeutic in humans.

Neuroprotective Benefit: May protect neurons from inflammation, oxidative stress, and ER-stress induced cell death. Has both intracellular and paracrine effects.

Aging and related health concerns: Decreases in MANF may contribute to age-related inflammation and organ damage. May promote pancreas regeneration in diabetes. Extends lifespan in flies.

Safety: Recombinant MANF has not been tested in humans. MANF therapy has generally been safe in preclinical studies, but would need to be administered directly into brain for neurodegenerative diseases, which carries its own safety risks.

Availability: Research use	**Dose**: Not established	**Chemical formula:** 183 aa **MW**: 20kDa  Source: RCSB PDB
Half-life: Information not available	**BBB**: recombinant protein not penetrant	
Clinical trials: None	**Observational studies**: MANF serum levels decrease in aging.	

What is it? Mesencephalic astrocyte-derived neurotrophic factor (MANF), also known as Arginine-rich, mutated in early-state tumors (ARMET) was originally identified as a gene that is highly mutated and upregulated in a variety of human cancers. It is an endoplasmic reticulum (ER) resident protein that is **upregulated in response to ER stress** as part of the adaptive unfolded protein response (UPR) [1]. MANF can also be secreted and exert paracrine cytoprotective effects. MANF may play a role in age-related inflammation and susceptibility of cells to stressors. In preclinical models recombinant MANF has been shown to have neuroprotective and anti-inflammatory effects. It is currently in development as a therapeutic for Parkinson's disease and retinal degeneration diseases.

Neuroprotective Benefit: May protect neurons from inflammation, oxidative stress, and ER-stress induced cell death. Has both intracellular and paracrine effects.

Types of evidence:

- Numerous laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function? None

Human research to suggest benefits to patients with dementia: None

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Protection against intracellular ER-stress: The exact mechanisms by which MANF exerts its neuroprotective effects are not fully understood because the cell receptors responsible for mediating its paracrine protective activity have not yet been identified. Intracellularly MANF is localized to the

ER, and after entering the Golgi complex can be secreted in response to decreases in ER calcium levels [2]. MANF **protects neurons from ER stress mediated apoptosis.** Within the ER, MANF interacts with the Hsp70 molecular chaperone GRP78, also known as BiP, which is a UPR protein upregulated in response to ER stress, and plays a critical role in proper protein folding [3]. The activity of GRP78 is regulated by ATPase activity, as it restricts protein folding in its ADP bound state and permits protein folding in its ATP bound state. MANF may promote protein folding homeostasis through the stabilization of the GRP78 ADP bound state [4].

Age-related declines in chaperone activity may increase the vulnerability of neurons to misfolded proteins and ER stress damage. Chaperones are also important for the maintenance and conformation of protein complexes involved in DNA binding, which can affect stress response related gene transcription. In mice, expression of the chaperone Hsc70 was found to decrease with age, which led to decreased levels of MANF and increased the vulnerability of Purkinje cells in the cerebellum [5]. Overexpression of MANF was found to be protective against Purkinje cell degeneration in this model. Therefore, maintenance of high levels of MANF **may help reduce the susceptibility of older neurons to stress-mediated damage.**

Anti-inflammatory: Animals with reduced levels of MANF show elevated inflammation [6]. In the retina, MANF was found to be protective by promoting the alternative activation of innate immune cells towards a pro-reparative state [7].

Antioxidant: The cytoprotective activity of MANF is largely attributed to its C-terminus. MANF protects against stress induced apoptosis, which is associated with a shift toward more anti-apoptotic Bcl2 and less pro-apoptotic Bax. The C-terminal SAP domain is homologous to the SAP domain of the Bax inhibitor Ku70 [8]. Some studies suggest that the neuroprotection is partly mediated by MANF's antioxidant activity [9; 10]. The C-terminus contains a CXXC (CKGC) motif **which can neutralize reactive oxygen species (ROS)** and prevent loss of mitochondrial membrane potential and caspase activation *in vitro* [11]. The cytoprotection is dependent on the presence of the cysteines, and is enhanced by their reduction to the thiol state. Reactive cysteines (thiols) are a common feature of many antioxidants, as they can activate Nrf2 and its associated antioxidant system.

Paracrine cytoprotection: While the C-terminus is important for cytoprotective activity, the N-terminus appears to be involved in facilitating the endocytic uptake of MANF, which is necessary for it to exert its intracellular effects [12]. MANF can bind the sulfatide 3-O-sulfogalactosylceramide, which is localized to outer cell membrane leaflets, and this interaction promotes endocytic uptake of MANF in *C. elegans.* Blocking the interaction with sulfatides blocks the ability of extracellular MANF to protect

against ER-stress mediated cell death. MANF likely associates with sulfatide in the Golgi prior to secretion, which can then enhance the endocytosis of MANF into target cells. This suggests that preincubation of recombinant MANF with sulfatides may enhance its *in vivo* neuroprotective efficacy.

Parkinson's Disease: Potential benefit (preclinical)

MANF was originally identified as a secreted neurotrophic factor with **preferential selectivity for dopaminergic neurons**. It was found to have higher selectivity for dopaminergic neurons at low and moderate concentrations, relative to other neurotrophic factors, BDNF and GDNF [13]. MANF mutant fly embryos have high levels of ER stress and extremely low levels of dopamine [14]. They also show alterations in Parkinson's disease (PD) associated genes and impaired lysosomal trafficking/function. Intrastriatal injection of recombinant human MANF (rhMANF) in rodents was found to be partially protective against behavioral deficits and the loss of dopaminergic neurons in the substantia nigra when administered prior to the neurotoxins 6-OHDA or MPTP [10; 15]. The neuroprotection may involve MANF's antioxidant activity, as MANF can activate Nrf2 and induce Nrf2 response genes in cell culture, and blocking Nrf2 mitigates the protective effects against these neurotoxins [9; 10]. This **anti-apoptotic and antioxidant activity** has been found be dependent on the Akt/PI3K signaling pathway [9]. MANF was also found to have better distribution in the striatum beyond the injection sites, relative to GDNF [15]. MANF may also offer benefits in PD by modulating dopamine release. In rat midbrain slices, MANF treatment led to presynaptic enhancement of GABAergic inhibition on dopaminergic neurons [16]. Intrastriatal injection of MANF, but not GDNF, into healthy rats was found to enhance stimulus-evoked dopamine release in the striatum within one week [17]. The effect was transitory, as the potentiation did not occur when tested 3 weeks after MANF administration, suggesting that repeated injections or a continuous infusion delivery system may be necessary for sustained effects.

Alzheimer's Disease: Potential benefit (preclinical)

Sulfatides, which may be key mediators of the paracrine neuroprotective effects of MANF, have been shown to be decreased in the brain and cerebrospinal fluid (CSF) of individuals with AD [18]. This may increase the vulnerability of neurons to Aβ induced ER stress. MANF and ER stress markers are upregulated in the brain of the APP/PS1 transgenic mouse model [19]. *In vitro*, rhMANF was able to reduce induction of ER stress markers and partially protect against Aβ mediated cytotoxicity. However, if MANF cannot be efficiently endocytosed then augmenting levels of extracellular MANF may be insufficient to protect neurons. Thus, due to the low endogenous levels of sulfatides, recombinant MANF therapy may only be effective if supplemented with sulfatides in AD patients.

Stroke/Traumatic Brain Injury: Potential benefit (preclinical)

MANF has been shown to be transiently upregulated in neurons, and to a lesser degree in glial cells, in response brain injury involving ischemia or ER stress [20; 21; 22; 23; 24; 25; 26]. Treatment with intracerebral rhMANF (5-20 ug) before or within 1 hour of ischemic stroke (MCAO), hemorrhagic stroke, or traumatic brain injury can reduce lesion size, and protect against neuronal loss, brain edema, BBB breakdown, and inflammation, while also enhancing functional recovery in rodents [20; 24; 25; 26; 27; 28]. **Protection may require administration of MANF close to time of damage,** as treatment starting 3 days after MCAO could modulate the immune response and promote functional recovery, but it had no effect on lesion size [29]. Furthermore, MANF was only partially protective, and one study found it less effective than edavarone [27]. However, MANF treatment may require a continuous infusion approach, thus acute treatment may have underestimated the potential benefits. Infusion of rhMANF into the peri-infarct region via canula (12 ul/day at 0.25 ug/ul) for two weeks promoted the migration of neural progenitor cells to the infusion site, and may promote their differentiation into neurons [30].

APOE4 interactions:

No clear role between ApoE and MANF has been established, however, one study found that ApoE regulates sulfatide homeostasis, such that higher levels of ApoE are associated with lower levels of sulfatides [18]. This suggests that ApoE status may affect the ability of neurons to take up extracellular MANF, which could impact the potential efficacy of recombinant MANF therapy.

Aging and related health concerns: Decreases in MANF may contribute to age-related inflammation and organ damage. May promote pancreas regeneration in diabetes. Extends lifespan in flies.

Types of evidence:

- 3 observational studies MANF serum levels (Aging, n=60; Type 2 diabetic adults, n=257; Type 1 diabetic children, n=186)
- Numerous laboratory studies

Lifespan: Potential benefit (in flies)

MANF expression levels have been found to modulate lifespan in flies [6; 31]. The degree of extension or shortening depends on which cell types are targeted. Lifespan was reduced by 11 to 24% in the context of ubiquitous, glial specific, and hepatocyte specific MANF deficiency; these flies also have

increased inflammation [6; 31]. Meanwhile, **lifespan was extended by 13 to 48% with MANF overexpression** in hepatocytes or fat bodies [6]. While levels of MANF have been found to decline with age in a variety of species, including humans [6], the ability of MANF to influence lifespan in mammals has not yet been established.

Liver Metabolism: Potential benefit (preclinical)

Serum MANF levels decrease with age from approximately 3.5 ng/ml at age 20-40 to approximately 2.25 ng/ml over age 60 ($P<0.01$) [6]. **Declines in MANF levels may promote age-related liver damage and inflammation.** Mice heterozygous for MANF develop progressive liver disease and steatosis, and patients with non-alcoholic fatty liver disease (NASH) were found to have lower circulating levels of MANF relative to age-matched controls [6]. These mice also show accelerated age-related inflammation. The effects on fat accumulation and inflammation-associated damage in the liver are mediated by different cell types, as the effect on liver fat accumulation could be recapitulated by MANF depletion specifically in hepatocytes, whereas the inflammatory damage could be induced by MANF depletion in Cx3cr1+ macrophages. Treatment with rhMANF (i.p. 0.7 mg/kg 3x/week for 5 weeks) reduced liver cytokine levels and age-related signs of liver damage in aged (20 month) mice. **MANF has also been implicated in mediating the liver rejuvenating effects of young blood.** In mice, heterochronic parabiosis (5 month and 20 month) produced liver rejuvenating effects in MANF dependent manner, as parabiosis with young mice deficient in MANF (heterozygotes) failed to offer liver protective benefits to the conjoined older mice. This suggests that the rejuvenating effects of young plasma therapy may be partially dependent on the presence of high levels of MANF.

Diabetes: Potential benefit (preclinical)

MANF deficient mice have chronic UPR activation in their pancreatic islets leading to reduced β-cell mass and severe progressive diabetes [32; 33]. **Pancreatic overexpression of MANF can enhance β-cell proliferation and regeneration** in the streptomycin diabetes model [32]. Loss of MANF leads to increased susceptibility of β-cells to inflammatory cytokine induced ER stress. Inflammatory cytokines can induce MANF secretion *in vitro*, which acts to mitigate their cytotoxicity through activation of Akt and inhibition of NF-kB signaling [33; 34; 35]. Newly diagnosed adults with Type 2 diabetes, and children with Type 1 diabetes were found to have elevated serum levels of MANF [36], and an inverse correlation between MANF serum levels and time from diagnosis was found in children with Type 1 diabetes [37]. This suggests that MANF may be upregulated early in the disease course as a protective response, which gets lost over time. Indeed, prolonged cytokine stress exposure can lead to the degradation of endogenous MANF [34]. rhMANF can partially protect human islet cells from cytokines *in vitro*,

through inhibition of NF-kB [34; 35]. Furthermore, MANF can induce global upregulation of gene expression and promote human β-cell proliferation in the context of TGFβ inhibition [35]. While hypothalamic MANF expression was shown to reduce insulin sensitivity in hypothalamic neurons [38], MANF serum levels were positively correlated with insulin sensitivity indices in prediabetic patients [36], suggesting that MANF may exert cell type specific effects, and would be expected to ameliorate not exacerbate insulin dysfunction in diabetics. This suggests that recombinant MANF therapy may have the potential to stop or reverse pancreatic β-cell loss in the context of diabetes.

Myocardial infarction: Potential benefit (preclinical)

MANF expression is induced in cardiac myocytes in response to myocardial infarction induced ischemia [2; 39]. The UPR protein ATF6 was shown to be important for the induction of MANF in response to ischemic stress in cardiac myocytes [39]. rhMANF infusion (300 ng/h/g) via an osmotic pump 24 hours prior to myocardial ischemia reduced infarct size by 44% in a mouse model [2]. This suggests that the presence of high levels of MANF close to the onset of an ischemic injury may be cardioprotective. However, the therapeutic window has not been established, so it is not clear whether rhMANF would also be protective after the onset of cardiac damage.

Macular Degeneration: Potential benefit (preclinical)

A mathematical model-based analysis examining how MANF influences processes associated with photoreceptor degeneration, and whether its addition has a significant effect on mitigating these processes found that MANF plays a key role in reducing apoptosis [40]. The authors concluded that irrespective of the underlying cause, MANF is likely to offer meaningful benefits when incorporated into a treatment program aimed at slowing photoreceptor degeneration. In mouse and fly models of photoreceptor degeneration, MANF was found to be upregulated in innate immune cells in response to the release of PDGF-A by damaged retinal cells [7]. **Innate immune cells adopted a protective M2-like state in response to MANF**, and intravitreal administration of rhMANF prior to the onset of retinal damage was able to **protect against subsequent photoreceptor apoptosis**. MANF is likely to be most beneficial when administered in conjunction with other therapies aimed at repairing pre-existing damage. When co-administered with cell replacement therapy, MANF enhanced integration of the injected cells and functional retinal recovery in mice.

Safety: Recombinant MANF has not been tested in humans. MANF therapy has generally been safe in preclinical studies, but would need to be administered directly into brain for neurodegenerative diseases, which carries its own safety risks.

Types of evidence:

- Numerous laboratory studies

Recombinant MANF therapy has not yet been tested in humans. Adverse events were not noted in any of the preclinical studies where rodents were administered rhMANF [2; 6; 7; 15; 24; 25; 27; 28; 29; 30; 32]. However, the longest use of rhMANF therapy was 5 weeks [6], so there is **no information available about possible long-term effects** of chronic recombinant MANF supplementation. Since recombinant MANF is not BBB penetrant, it needs to be administered directly into the brain for neurodegenerative conditions, thus complications associated with this delivery system is one of the biggest potential safety concerns at this time. A related neurotrophic factor, CDNF, is currently being tested in a Phase 1/2 clinical trial in Europe by Herantis Pharma (NCT03295786). CDNF is being administered to PD patients (n=18) using an implanted Reinshaw drug delivery system in monthly brain infusions for 6 months. The preliminary results from the first few patients suggest that the system is safe and well-tolerated (Press release). The results from this trial may influence the feasibility of using a similar strategy for MANF.

Although a rodent study indicated that extracellular rhMANF did not significantly impact insulin signaling in hypothalamic neurons, the study did not look at chronic administration [38]. Intracellular expression of MANF in hypothalamic neurons in mice was found to promote food consumption and reduced insulin sensitivity. Since secreted MANF can be taken up into cells, it is possible that depending on the way recombinant MANF is modified that it could be taken up by hypothalamic neurons and induce similar hyperphagic activity as endogenous MANF. Therefore, it may be necessary to carefully restrict the localization of recombinant of MANF infusion in the brain.

Some preclinical studies indicated that there is a U-shaped neuroprotective dose response to intrastriatal MANF administration [15; 28]. Similar dose responses have been seen with other growth factors, such as GDNF, indicating that an optimal therapeutic dose will need to be established, and precautions will be necessary to ensure that the therapeutic dose is not exceeded in the context of a continuous infusion delivery system.

Sources and dosing:

Recombinant human MANF is available for research use from commercial suppliers. Formulations for human use are currently in development by MANF therapeutics, but have not yet been clinically validated.

Research underway:

There are currently no clinical trials testing recombinant MANF therapy.

MANF therapeutics, which is a subsidiary of Amarantus BioScience, has acquired the IP necessary to develop MANF as a therapeutic. Their initial focus has been on retinal degenerative diseases and Parkinson's disease. They were granted Orphan drug designation by the FDA for retinitis pigmentosa in 2014 and retinal arterial occlusion in 2015. They initiated IND-enabling studies for MANF (ARMS-001) in glaucoma and retinitis pigmentosa in 2015, which were halted for unknown reasons. These studies were restarted in 2018. In early 2019 they received a patent allowance for the use of MANF therapy for Parkinson's in Europe and Diabetes in Japan.

Search terms:

Pubmed, Google: MANF or ARMET +

- Alzheimer's disease, Parkinson's disease, stroke, aging, lifespan, cardiovascular, diabetes, inflammation, safety, recombinant MANF therapy

Websites visited for MANF:

- PubChem

References:

1. Kim Y, Park S-J, Chen YM (2017) Mesencephalic astrocyte-derived neurotrophic factor (MANF), a new player in endoplasmic reticulum diseases: structure, biology, and therapeutic roles. *Translational research : the journal of laboratory and clinical medicine* 188, 1-9.https://www.ncbi.nlm.nih.gov/pubmed/28719799 https://www.ncbi.nlm.nih.gov/pmc/PMC5601018/

2. Glembotski CC, Thuerauf DJ, Huang C *et al.* (2012) Mesencephalic astrocyte-derived neurotrophic factor protects the heart from ischemic damage and is selectively secreted upon sarco/endoplasmic reticulum calcium depletion. *The Journal of biological chemistry* 287, 25893-25904.https://www.ncbi.nlm.nih.gov/pubmed/22637475 https://www.ncbi.nlm.nih.gov/pmc/PMC3406674/

3. Lindström R, Lindholm P, Kallijärvi J *et al.* (2016) Exploring the Conserved Role of MANF in the Unfolded Protein Response in Drosophila melanogaster. *PLOS ONE* 11, e0151550.https://doi.org/10.1371/journal.pone.0151550

4. Yan Y, Rato C, Rohland L *et al.* (2019) MANF antagonizes nucleotide exchange by the endoplasmic reticulum chaperone BiP. *Nature communications* 10, 541-541.https://www.ncbi.nlm.nih.gov/pubmed/30710085 https://www.ncbi.nlm.nih.gov/pmc/PMC6358605/

5. Yang S, Huang S, Gaertig MA *et al.* (2014) Age-dependent decrease in chaperone activity impairs MANF expression, leading to Purkinje cell degeneration in inducible SCA17 mice. *Neuron* 81, 349-365.https://www.ncbi.nlm.nih.gov/pubmed/24462098 https://www.ncbi.nlm.nih.gov/pmc/PMC4863472/

6. Sousa-Victor P, Neves J, Cedron-Craft W *et al.* (2019) MANF regulates metabolic and immune homeostasis in ageing and protects against liver damage. *Nature Metabolism* 1, 276-290.https://doi.org/10.1038/s42255-018-0023-6

7. Neves J, Zhu J, Sousa-Victor P *et al.* (2016) Immune modulation by MANF promotes tissue repair and regenerative success in the retina. *Science (New York, NY)* 353, aaf3646-aaf3646.https://www.ncbi.nlm.nih.gov/pubmed/27365452 https://www.ncbi.nlm.nih.gov/pmc/PMC5270511/

8. Hellman M, Arumäe U, Yu L-y *et al.* (2011) Mesencephalic astrocyte-derived neurotrophic factor (MANF) has a unique mechanism to rescue apoptotic neurons. *The Journal of biological chemistry* 286, 2675-2680.https://www.ncbi.nlm.nih.gov/pubmed/21047780 https://www.ncbi.nlm.nih.gov/pmc/PMC3024763/

9. Zhang J, Tong W, Sun H *et al.* (2017) Nrf2-mediated neuroprotection by MANF against 6-OHDA-induced cell damage via PI3K/AKT/GSK3β pathway. *Experimental Gerontology* 100, 77-86.http://www.sciencedirect.com/science/article/pii/S0531556517306241

10. Liu Y, Zhang J, Jiang M *et al.* (2018) MANF improves the MPP(+)/MPTP-induced Parkinson's disease via improvement of mitochondrial function and inhibition of oxidative stress. *American journal of translational research* 10, 1284-1294.https://www.ncbi.nlm.nih.gov/pubmed/29887945 https://www.ncbi.nlm.nih.gov/pmc/PMC5992546/

11. Božok V, Yu L-Y, Palgi J *et al.* (2018) Antioxidative CXXC Peptide Motif From Mesencephalic Astrocyte-Derived Neurotrophic Factor Antagonizes Programmed Cell Death. *Frontiers in cell and developmental biology* 6, 106-106.https://www.ncbi.nlm.nih.gov/pubmed/30234112 https://www.ncbi.nlm.nih.gov/pmc/PMC6132022/

12. Bai M, Vozdek R, Hnízda A *et al.* (2018) Conserved roles of C. elegans and human MANFs in sulfatide binding and cytoprotection. *Nature communications* 9, 897-897.https://www.ncbi.nlm.nih.gov/pubmed/29497057 https://www.ncbi.nlm.nih.gov/pmc/PMC5832864/

13. Petrova P (2003) MANF: a new mesencephalic, astrocyte-derived neurotrophic factor with selectivity for dopaminergic neurons. *Journal of molecular neuroscience* 20, 173-188

14. Palgi M, Greco D, Lindström R *et al.* (2012) Gene expression analysis of Drosophilaa Manf mutants reveals perturbations in membrane traffic and major metabolic changes. *BMC genomics* 13, 134-134.https://www.ncbi.nlm.nih.gov/pubmed/22494833 https://www.ncbi.nlm.nih.gov/pmc/PMC3364883/

15. Voutilainen MH, Bäck S, Pörsti E *et al.* (2009) Mesencephalic Astrocyte-Derived Neurotrophic Factor Is Neurorestorative in Rat Model of Parkinson's Disease. *The Journal of Neuroscience* 29, 9651-9659.http://www.jneurosci.org/content/jneuro/29/30/9651.full.pdf

16. Zhou C, Xiao C, Commissiong JW *et al.* (2006) Mesencephalic astrocyte-derived neurotrophic factor enhances nigral γ-aminobutyric acid release. *NeuroReport* 17, 293-297.https://journals.lww.com/neuroreport/Fulltext/2006/02270/Mesencephalic_astrocyte_derived_neurotrophic.13.aspx

17. Renko J-M, Bäck S, Voutilainen MH *et al.* (2018) Mesencephalic Astrocyte-Derived Neurotrophic Factor (MANF) Elevates Stimulus-Evoked Release of Dopamine in Freely-Moving Rats. *Molecular neurobiology* 55, 6755-6768.https://www.ncbi.nlm.nih.gov/pubmed/29349573 https://www.ncbi.nlm.nih.gov/pmc/PMC6061195/

18. Han X (2010) The pathogenic implication of abnormal interaction between apolipoprotein E isoforms, amyloid-beta peptides, and sulfatides in Alzheimer's disease. *Molecular neurobiology* 41, 97-106.https://www.ncbi.nlm.nih.gov/pubmed/20052565 https://www.ncbi.nlm.nih.gov/pmc/PMC2877150/

19. Xu S, Di Z, He Y *et al.* (2019) Mesencephalic astrocyte-derived neurotrophic factor (MANF) protects against Aβ toxicity via attenuating Aβ-induced endoplasmic reticulum stress. *Journal of neuroinflammation* 16, 35-35.https://www.ncbi.nlm.nih.gov/pubmed/30760285 https://www.ncbi.nlm.nih.gov/pmc/PMC6373169/

20. Yu Y-Q, Liu L-C, Wang F-C *et al.* (2010) Induction profile of MANF/ARMET by cerebral ischemia and its implication for neuron protection. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism* 30, 79-91.https://www.ncbi.nlm.nih.gov/pubmed/19773801 https://www.ncbi.nlm.nih.gov/pmc/PMC2949098/

21. Lindholm P, Peränen J, Andressoo J-O *et al.* (2008) MANF is widely expressed in mammalian tissues and differently regulated after ischemic and epileptic insults in rodent brain. *Molecular and Cellular Neuroscience* 39, 356-371.http://www.sciencedirect.com/science/article/pii/S1044743108001942

22. Airavaara M, Chiocco MJ, Howard DB *et al.* (2010) Widespread cortical expression of MANF by AAV serotype 7: localization and protection against ischemic brain injury. *Experimental neurology* 225, 104-113.https://www.ncbi.nlm.nih.gov/pubmed/20685313 https://www.ncbi.nlm.nih.gov/pmc/PMC2925275/

23. Shen Y, Sun A, Wang Y *et al.* (2012) Upregulation of mesencephalic astrocyte-derived neurotrophic factor in glial cells is associated with ischemia-induced glial activation. *Journal of neuroinflammation* 9, 254-254.https://www.ncbi.nlm.nih.gov/pubmed/23173607 https://www.ncbi.nlm.nih.gov/pmc/PMC3576245/

24. Gao L, Xu W, Fan S *et al.* (2018) MANF attenuates neuronal apoptosis and promotes behavioral recovery via Akt/MDM-2/p53 pathway after traumatic spinal cord injury in rats. *BioFactors* 44, 369-386.https://iubmb.onlinelibrary.wiley.com/doi/abs/10.1002/biof.1433

25. Li Q-X, Shen Y-X, Ahmad A *et al.* (2018) Mesencephalic Astrocyte-Derived Neurotrophic Factor Prevents Traumatic Brain Injury in Rats by Inhibiting Inflammatory Activation and Protecting the Blood-Brain Barrier. *World Neurosurgery* 117, e117-e129.http://www.sciencedirect.com/science/article/pii/S1878875018311562

26. Xu W, Gao L, Li T *et al.* (2018) Mesencephalic Astrocyte-Derived Neurotrophic Factor (MANF) Protects Against Neuronal Apoptosis via Activation of Akt/MDM2/p53 Signaling Pathway in a Rat Model of Intracerebral Hemorrhage. *Frontiers in molecular neuroscience* 11, 176-176.https://www.ncbi.nlm.nih.gov/pubmed/29896089 https://www.ncbi.nlm.nih.gov/pmc/PMC5987019/

27. Wang X-Y, Song M-M, Bi S-X *et al.* (2016) MRI Dynamically Evaluates the Therapeutic Effect of Recombinant Human MANF on Ischemia/Reperfusion Injury in Rats. *International journal of molecular sciences* 17, 1476.https://www.ncbi.nlm.nih.gov/pubmed/27608005 https://www.ncbi.nlm.nih.gov/pmc/PMC5037754/

28. Airavaara M, Shen H, Kuo C-C *et al.* (2009) Mesencephalic astrocyte-derived neurotrophic factor reduces ischemic brain injury and promotes behavioral recovery in rats. *The Journal of comparative neurology* 515, 116-124.https://www.ncbi.nlm.nih.gov/pubmed/19399876 https://www.ncbi.nlm.nih.gov/pmc/PMC2723810/

29. Mätlik K, Anttila JE, Kuan-Yin T *et al.* (2018) Poststroke delivery of MANF promotes functional recovery in rats. *Science advances* 4, eaap8957-eaap8957.https://www.ncbi.nlm.nih.gov/pubmed/29806020 https://www.ncbi.nlm.nih.gov/pmc/PMC5966223/

30. Tseng K-Y, Anttila JE, Khodosevich K *et al.* (2018) MANF Promotes Differentiation and Migration of Neural Progenitor Cells with Potential Neural Regenerative Effects in Stroke. *Molecular therapy : the journal of the American Society of Gene Therapy* 26, 238-255.https://www.ncbi.nlm.nih.gov/pubmed/29050872 https://www.ncbi.nlm.nih.gov/pmc/PMC5763030/

31. Walkowicz L, Kijak E, Krzeptowski W *et al.* (2017) Downregulation of DmMANF in Glial Cells Results in Neurodegeneration and Affects Sleep and Lifespan in Drosophila melanogaster. *Frontiers in neuroscience* 11, 610-610.https://www.ncbi.nlm.nih.gov/pubmed/29163014 https://www.ncbi.nlm.nih.gov/pmc/PMC5673640/

32. Lindahl M, Danilova T, Palm E *et al.* (2014) MANF Is Indispensable for the Proliferation and Survival of Pancreatic β Cells. *Cell Reports* 7, 366-375.http://www.sciencedirect.com/science/article/pii/S2211124714002010

33. Danilova T, Belevich I, Li H *et al.* (2019) MANF Is Required for the Postnatal Expansion and Maintenance of Pancreatic β-Cell Mass in Mice. *Diabetes* 68, 66-80.http://diabetes.diabetesjournals.org/content/diabetes/68/1/66.full.pdf

34. Cunha DA, Cito M, Grieco FA *et al.* (2017) Pancreatic β-cell protection from inflammatory stress by the endoplasmic reticulum proteins thrombospondin 1 and mesencephalic astrocyte-derived neutrotrophic factor (MANF). *The Journal of biological chemistry* 292, 14977-14988.https://www.ncbi.nlm.nih.gov/pubmed/28698383 https://www.ncbi.nlm.nih.gov/pmc/PMC5592674/

35. Hakonen E, Chandra V, Fogarty CL *et al.* (2018) MANF protects human pancreatic beta cells against stress-induced cell death. *Diabetologia* 61, 2202-2214.https://www.ncbi.nlm.nih.gov/pubmed/30032427 https://www.ncbi.nlm.nih.gov/pmc/PMC6133171/

36. Wu T, Zhang F, Yang Q *et al.* (2017) Circulating mesencephalic astrocyte-derived neurotrophic factor is increased in newly diagnosed prediabetic and diabetic patients, and is associated with insulin resistance. *Endocrine Journal* 64, 403-410

37. Galli E, Härkönen T, Sainio MT *et al.* (2016) Increased circulating concentrations of mesencephalic astrocyte-derived neurotrophic factor in children with type 1 diabetes. *Scientific reports* 6, 29058-29058.https://www.ncbi.nlm.nih.gov/pubmed/27356471 https://www.ncbi.nlm.nih.gov/pmc/PMC4928177/

38. Yang S, Yang H, Chang R *et al.* (2017) MANF regulates hypothalamic control of food intake and body weight. *Nature communications* 8, 579-579.https://www.ncbi.nlm.nih.gov/pubmed/28924165 https://www.ncbi.nlm.nih.gov/pmc/PMC5603516/

39. Tadimalla A, Belmont PJ, Thuerauf DJ *et al.* (2008) Mesencephalic astrocyte-derived neurotrophic factor is an ischemia-inducible secreted endoplasmic reticulum stress response protein in the heart. *Circulation research* 103, 1249-1258.https://www.ncbi.nlm.nih.gov/pubmed/18927462 https://www.ncbi.nlm.nih.gov/pmc/PMC2746824/

40. Wirkus S, Camacho ET, Lenhart S *et al.* (2019) Optimal control with MANF treatment of photoreceptor degeneration.https://doi.org/10.1093/imammb/dqz003

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