MANF and CDNF as Regulators of Cellular Stress Pathways in Preclinical Models of Neurodegeneration: A Systematic Scoping Review

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Supplemental Materials

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations <1996 to September 26, 2025>

Search Strategy:

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1 (Mesencephalic astrocyte-derived neurotrophic factor or MANF).ti,ab,kf. (403)

2 (Cerebral Dopamine Neurotrophic Factor or CDNF).ti,ab,kf. (171)

3 ((MANF or CDNF) and (neurotrophic factor* or neuroprotect* or "dopaminergic neuron*")).ti,ab,kf. (379)

4 ((Endoplasmic Reticulum Stress or ER stress or unfolded protein response or UPR) and (MANF or CDNF)).ti,ab,kf. (197)

5 ((dopaminergic neuron* or dopamine neuron* or mesencephalon or substantia nigra) and (MANF or CDNF)).ti,ab,kf. (120)

6 or/1-5 (509)

5 limit 6 to (english language and yr="2005 -2025") (505)

Database: Embase <1996 to 2025 September 25>

Search Strategy:

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1 mesencephalic astrocyte-derived neurotrophic factor.mp. (598)

2 MANF.ti,ab,kf. (519)

3 (Cerebral Dopamine Neurotrophic Factor or CDNF).ti,ab,kf. (243)

4 (exp neurotrophic factor/ or (neurotrophic factor?).ti,ab,kf.) and ((cerebral dopamine or Mesencephalic astrocyte-derived or Endoplasmic Reticulum Stress or ER stress).ti,ab. or exp Endoplasmic Reticulum Stress/) (1230)

5 or/1-4 (1535)

6 limit 5 to (English language and yr="2005 -2025") (1506)

Web of Science Sept 29, 2025

1. TS=(Mesencephalic astrocyte-derived neurotrophic factor or MANF) OR TI=(Mesencephalic astrocyte-derived neurotrophic factor or MANF) OR AB=(Mesencephalic astrocyte-derived neurotrophic factor or MANF) (521)

2. TS=(Cerebral Dopamine Neurotrophic Factor or CDNF) OR TI=(Cerebral Dopamine Neurotrophic Factor or CDNF) OR AB=(Cerebral Dopamine Neurotrophic Factor or CDNF)

3. neurotrophic factor* or nerve growth factor* (Abstract) and central dopamine or Mesencephalic astrocyte-derived or Endoplasmic Reticulum Stress or ER stress (Abstract)

4. #1 OR #2 OR #3

5. #1 OR #2 OR #3 and English (Languages)

6. #1 OR #2 OR #3 and English (Languages) and 2005 or 2006 or 2007 or 2008 or 2009 or 2010 or 2012 or 2013 or 2014 or 2015 or 2016 or 2017 or 2018 or 2019 or 2020 or 2021 or 2022 or 2023 or 2024 or 2025 (Publication Years)

1026 documents

Supplementary Fig. S1 Search String

Search strategies used across Ovid MEDLINE, Embase, and Web of Science to identify studies investigating mesencephalic astrocyte-derived neurotrophic factor (MANF) and cerebral dopamine neurotrophic factor (CDNF) in neurodegeneration. Search terms included combinations of “MANF,” “CDNF,” “neurotrophic factor,” “dopaminergic neurons,” and endoplasmic reticulum (ER) stress-related terms. Searches were limited to English-language publications from 2005 to 2025.

Supplementary Table S1 Eligibility Criteria for Title and Abstract Screening.

Eligibility criteria applied during initial screening of titles and abstracts. Studies were included if they involved preclinical animal or cell culture models investigating MANF/CDNF in neurodegenerative contexts, with relevant neuronal, behavioural, or stress-related outcomes.

Studies were excluded if they involved human participants, non-neuronal models, unrelated neurotrophic factors, or lacked appropriate comparators or neurodegenerative relevance.

	Include	Exclude
Population	Pre-clinical animal and cell culture models	Human and non-neuronal studies.
Intervention	Studies involving MANF/CDNF (genetic manipulation, recombinant protein, measurement of levels/localization)	Studies focused on other neurotrophic factors or non-neurodegenerative contexts.
Comparator	Require some form of control or comparison (wild-type vs. mutant, treated vs. untreated)	No comparator.
Outcomes	Abstracts suggest neuronal/neuroprotective, behavioural, stress-related, or lysosomal/autophagy outcomes	Unrelated to neurodegeneration.
Study Type	Original research	Reviews, conference abstracts, and clinical trials.

Supplementary Table S2 Eligibility Criteria for Full-Text Review.

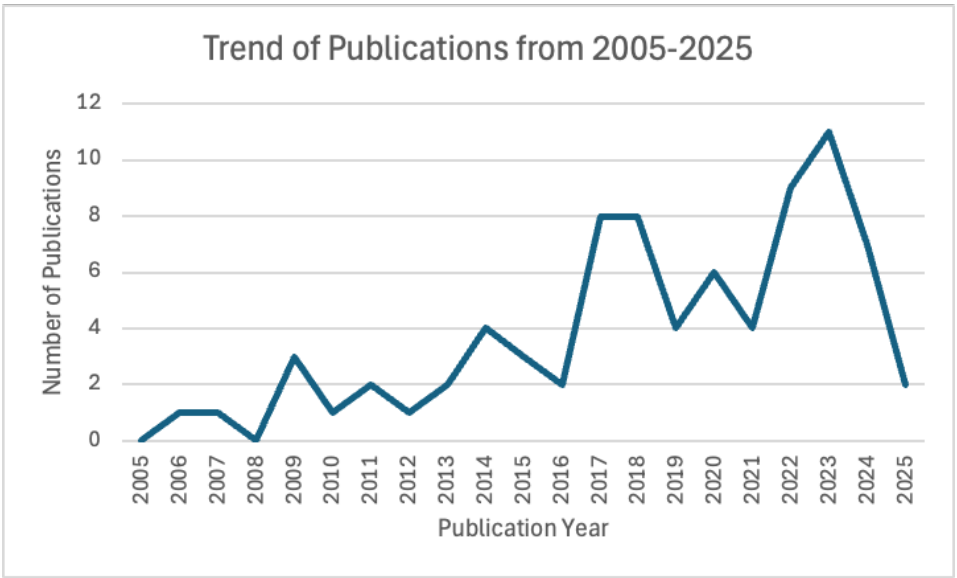
Detailed inclusion and exclusion criteria applied during full-text screening, including study design, intervention type, and neurodegeneration-specific outcomes.

	Include	Exclude
Population	• Pre-clinical animal models • Cell culture models	• Studies involving human subjects • Non-neuronal models
Intervention/ Exposure	• Changes in MANF/CDNF gene and protein 1. Genetic manipulation (knockout, knockdown, overexpression) 2. Recombinant MANF/CDNF administration • Studies assessing MANF/CDNF levels and localization	• Studies on other neurotrophic factors without MANF/CDNF involvement • Studies involving MANF/CDNF but in non-neurodegenerative conditions (e.g., metabolic disease, cardiovascular health)

	• Studies describing any modifications to MANF/CDNF	• Studies involving changes in MANF/CDNF but not measuring effects on neurons
Comparator/ Context	• Wild-type vs. MANF/CDNF-models • MANF/CDNF-treated vs. untreated conditions • Comparative analysis across different neurodegenerative disease models	• Studies without a control or comparative group • Studies that do not analyze MANF/CDNF changes in a neurodegeneration context • Studies that lack quantitative data on MANF/CDNF treatments and their effects
Outcome	• Studies reporting the	• Studies only

	effect of MANF/CDNF changes on neuronal health regarding ER stress. ● Studies assessing the impact of MANF/CDNF on motor function improvement (e.g., motor coordination, balance, or motor learning abilities in neurodegenerative models). ● Studies that specifically evaluate the effects of MANF/CDNF on dopaminergic neuron health (e.g., survival, differentiation, function, and	measuring MANF/CDNF in non-neurodegenerative contexts ● Studies that do not include relevant motor function, behavioural, or dopaminergic neuron health outcomes in the context of MANF/CDNF manipulation.

	protection of dopaminergic neurons). ● Studies assessing MANF/CDNF in relation to neurodegenerative disease progression	
Study Characteristics	● Original research ● Neuroprotection; behavioural and morphological criteria	● Non-empirical Studies ● Studies without Neuroprotection or Neurodegeneration Focus ● Reviews ● Conference studies ● Randomized control studies ● Clinical trials ● Studies lacking quantitative measures ● Studies before 2005



Supplementary Figure S2 Temporal trend in MANF/CDNF publications from 2006-2025. Line graph showing the increase in publication frequency across four-time intervals (2006-2010, 2011-2015, 2016-2020, 2021-2025). A consistent upward trajectory is evident, with the highest output in the 2021–2025 period. Data collection was completed in early 2025, which may limit the apparent growth in this final interval, as publications from late 2024 to 2025 are underrepresented.

Supplementary Table S3. Interventions, Populations, Comparator, and Key Finding.

Summary of included studies detailing intervention type, experimental model, comparator conditions, primary outcomes, and study aims across preclinical models, highlighting the role of MANF and CDNF in neuroprotection, dopaminergic neuron survival, and motor and behavioural outcomes.

Author, Year of Publication	Intervention Type	Population	Comparator	Primary Outcomes Measured *	Primary Study Aim
1. Kemppainen, et al., 2015 [72]	Recombinant CDNF administration	Mice/ APP/PS1 transgenic mouse model of Alzheimer's disease (AD) and wild-type controls.	APP/PS1 transgenic mice (AD model) vs. wild-type controls	General behaviour and DA survival improvement.	To evaluate whether intrahippocampal administration of CDNF improves long-term memory in APP/PS1 transgenic mice modelling Alzheimer's disease and wild-type mice.
2. Garea-Rodriguez et al., 2016 [43]	Recombinant CDNF vs GDNF protein infusion	Marmoset, Callithrix jacchus, 6-OHDA lesion model of PD.	CDNF vs. GDNF treatment in PD primate model	Motor function improvement.	To compare the effects of CDNF and GDNF on dopaminergic recovery in a nonhuman primate model of PD.
3. Nasrolahi et al., 2019 [16]	Recombinant CDNF administration	Wistar rats; 6-OHDA model of PD in rats	PD model rats treated with CDNF vs. controls.	Behavioural improvement.	To assess whether intracerebroventricular or intraventricular administration of CDNF promotes proliferation and migration of endogenous neural progenitor cells from the subventricular zone to the striatum, and improves motor function, in a 6-hydroxydopamine-induced PD rat model.
4.Voutilainen et al., 2011 [30]	Recombinant CDNF administration	Male Wistar rats with unilateral 6-OHDA lesion in the left striatum.	6-OHDA lesion rat model with chronic CDNF infusion vs. vehicle	Motor function improvement, and DA survival improvement.	To determine whether chronic intrastriatal infusion of CDNF (over 2 weeks) prevents behavioural deficits and preserves nigrostriatal dopamine neurons in a unilateral 6-OHDA rat model of PD.
5. Jiaming & Niu et al., 2015 [52]	Stem cell delivery of CDNF	48 female Sprague–Dawley rats, 6-OHDA-lesioned model.	Bone marrow MSCs expressing CDNF via different administration routes vs. saline controls	Motor function improvement and DA survival improvement.	To compare the neuroprotective efficacy of CDNF-expressing bone marrow-derived mesenchymal stem cells administered via intrastriatal, intraventricular, or intravenous routes in a 6-OHDA-induced rat model of PD.
6. Zhang et al., 2024 [28]	Endogenous MANF overexpression	Speices: C57BL/6J mice, Model: 5xFAD mice (Alzheimer's model), APP/PS1 mice, MANF-transgenic	Alzheimer's disease models with increased MANF expression vs. controls	Behavioural improvement.	To examine how increased MANF expression contributes to synapse loss and cognitive impairment in Alzheimer's disease.

		mice			
7. Eesmaa et al., 2022 [32]	Endogenous CDNF upregulation	Mouse primary neuron cultures, HEK293 and INS1 cell lines, ICR (CD-1) mice, TH-EGFP transgenic mice.	CDNF-treated neurons vs. untreated or vehicle-treated neurons	DA survival improvement.	To elucidate the mechanism by which CDNF interacts with ER chaperones and depends on UPR sensors (IRE1α, PERK) to promote neuronal survival under ER stress conditions.
8. Singh et al., 2023 [35]	No intervention (study design, model creation only)	Mouse primary midbrain neuron cultures from E13.5 embryos.	Combined alpha-synuclein + 6-OHDA-treated cultures vs. controls	DA survival improvement.	To develop a combined α-synuclein and 6-OHDA model of dopaminergic neuron degeneration and assess CDNF's protective effects.
9. Bäck et al., 2013 [49]	Gene therapy: AAV2-CDNF delivery	Species: Adult male Wistar rats; Model: 6-OHDA striatal lesion of PD.	AAV2-CDNF gene therapy vs. AAV2-GFP and untreated controls	DA neuronal survival and motor function improvement.	To assess the neuroprotective and functional effects of AAV2-CDNF gene therapy in a 6-OHDA rat model of PD.
10. Kovaleva et al., 2023 [29]	Endogenous MANF expression regulation	Rat (Wistar) model of PD using 6-OHDA lesion; HEK293 and primary midbrain neurons.	MANF manipulation (KO or overexpression) vs. wild-type controls	DA neuronal survival and motor function improvement.	To determine whether MANF promotes neuronal survival and regulates the unfolded protein response by interacting with the ER stress sensor IRE1α.
11. Zhang et al., 2018 [27]	Recombinant CDNF administration	Rat (Sprague-Dawley) model of stroke MCAO; OGD model for in vitro.	CDNF-treated neurons vs. untreated controls under cerebral ischemia	DA neuronal survival and motor function improvement.	To evaluate the neuroprotective effects of CDNF against cerebral ischemia via the ER stress pathway.

12. Pakarinen et al., 2020 [83]	Endogenous MANF knockout (knockout model)	Species: C57BL/6J mice (wild-type and MANF-deficient mice) Model: MANF knockout mouse models, using NestinCre/1 transgenic mice.	MANF knockout mice vs. wild-type controls	DA neuronal survival and motor function improvement.	To determine if deletion of endogenous MANF in the mouse midbrain triggers prolonged UPR activation without causing dopamine neuron degeneration
13.Fernandez-Parilla et al., 2022 [66]	Gene Therapy: Viral or Protein Complex Delivery	Male Wistar rats; 6-OHDA lesion model of PD.	Neurotensin-CDNF transfection vs. untreated controls in 6-OHDA model	DA neuronal survival and motor function improvement.	To determine if targeted CDNF gene delivery to dopamine neurons via neurotensin-polyplex nanoparticles can reverse 6-OHDA–induced nigrostriatal degeneration in rats.
14. Zhang et al., 2018 [80]	Recombinant MANF protein treatment in *C. elegans*	Species: *C. elegans* Model: Human α-synuclein-induced PD model in *C. elegans.*	*C. elegans* PD model with MANF manipulation vs. controls	DA neuronal survival and motor function improvement.	To assess if MANF protects dopaminergic neurons and improves locomotion in a *C. elegans* α-synuclein PD model by modulating ER stress and autophagy pathways.
15. Walkowicz et al., 2017[31]	Endogenous DmMANF knockdown in Drosophila	Species: Drosophila melanogaster (fruit fly) Model: DmMANF knockdown using RNA interference (RNAi).	DmMANF knockdown in glial cells vs. neurons and controls	DA neuronal survival and motor function improvement.	To investigate whether glial-specific downregulation of DmMANF leads to neurodegeneration and alters sleep patterns and lifespan in *Drosophila melanogaster*.
16. Xu et al., 2018 [87]	Recombinant MANF administration	Sprague-Dawley rats; autologous blood injection model of ICH.	MANF-treated intracerebral hemorrhage rat model vs. vehicle	DA neuronal survival and motor function improvement.	To determine whether MANF protects neurons from apoptosis via activation of the Akt/MDM2/p53 signaling pathway in a rat model of intracerebral hemorrhage.

17. Hellman et al., 2011 [36]	Recombinant MANF treatment in cell culture	Species: SCG neurons (mouse sympathetic neurons). Model: Apoptosis induced by NGF deprivation, etoposide, or staurosporine	MANF treatment vs. untreated apoptotic neurons	DA neuronal survival.	To determine how MANF rescues apoptotic neurons via its structurally unique C-terminal SAP-like domain, which binds and inhibits the pro-apoptotic protein Bax, thereby promoting intracellular neuroprotection.
18. Zhou et al., 2016 [91]	Recombinant Protein Administration (CDNF injection)	Wistar rat primary hippocampal cells	CDNF treatment vs. Aβ-induced ER stress in rat hippocampal cells	DA neuronal survival.	To evaluate whether CDNF mitigates Aβ25-35-induced ER stress and early synaptotoxicity in rat hippocampal neurons.
19. Tsybko et al., 2024 [92]	Recombinant CDNF protein injection	C57BL/6 mice.	CDNF-treated vs. untreated or vehicle-treated animals	Behavioural improvement.	To investigate whether intracerebroventricular CDNF produces anxiolytic, antidepressant-like, and procognitive effects in mice by modulating serotonin turnover, neuronal activation, and UPR-related gene expression.
20. Wang et al., 2017 [68]	AAV-CDNF gene therapy	6-OHDA-induced Parkinsonian rat model.	AAV8-CDNF intrastriatal delivery vs. vehicle-treated parkinsonian rats	DA neuronal survival and motor function improvement.	To assess the efficacy of AAV8-CDNF gene therapy at different stages of PD progression in 6-OHDA rat models.
21. Zhang et al., 2017 [95]	Recombinant MANF administration	Species: SH-SY5Y cells (human neuroblastoma cell line).	MANF treatment vs. 6-OHDA cell damage controls	DA survival improvement.	To investigate whether MANF protects cells from 6–OHDA–induced damage by activating the Nrf2 pathway via PI3K/Akt/GSK3β signaling.
22. Richman et al., 2018 [22]	Endogenous Expression Modification (Knockout/Overexpression)	*C. elegans* (nematode model for neurodegeneration).	Wild-type vs. manf-1 mutant *C. elegans*	DA survival improvement.	To determine whether the *C. elegans* MANF homolog (manf-1) is essential for dopaminergic neuron survival and ER unfolded protein response maintenance.
23. Xu et al., 2019 [37]	Recombinant MANF administration	APP/PS1 transgenic mice, rat cortical	MANF-treated Alzheimer's model vs.	DA survival improvement.	To test whether MANF protects against Aβ-induced neurotoxicity by reducing endoplasmic reticulum stress in neuronal

		neurons, SH-SY5Y cell line.	untreated controls		models.
24. De Lorenzo et al., 2023 [38]	Recombinant CDNF protein administration	Species: Rats (TDP43-M337V), Mice (SOD1-G93A, TDP43-M337V)	CDNF treatment in ALS models vs. untreated controls	Motor function improvement.	To determine whether intracerebroventricular administration of CDNF mitigates ER stress and rescues motor neurons, improving motor behaviour across multiple ALS rodent models.
25. Tseng et al., 2022 [69]	Combination therapy using CDNF protein treatment and fetal ventral mesencephalic graft transplantation.	Hemiparkinsonian rat model.	CDNF treatment combined with fetal VM graft transplantation vs. graft alone	DA survival improvement and motor function improvement.	To determine whether CDNF co-administration enhances survival, integration, and functional recovery of fetal ventral mesencephalic grafts in hemiparkinsonian rats by modulating microglia/macrophage activation.
26. Shabani et al., 2022 [86]	Recombinant CDNF administration	Species: Mice (8–12 weeks old, male).	Photothrombotic stroke mouse model with CDNF vs. untreated controls	Motor function and behavioural improvement.	To assess whether CDNF promotes neuroblast proliferation, migration, and differentiation after stroke in a mouse model.
27. Stepanova et al., 2020 [45]	recombinant CDNF protein injection	Species: Rats (adult male Wistar rats, 250–300 g). Model: Quinolinic acid (QA)-induced model of Huntington's disease (HD).	CDNF-treated vs. quinolinic acid toxicity models	Motor function and behavioural improvement.	To investigate whether CDNF protects against quinolinic acid-induced toxicity in in vitro and in vivo Huntington's disease models.
28. Zhou, et al., 2006 [78]	Recombinant MANF effect on neurotransmitter release	Species: Sprague-Dawley rat Model: Primary dopaminergic neuron model	MANF-treated vs. untreated rat models	DA survival improvement.	To assess whether MANF enhances GABA release onto SNa dopamine neurons.

29. Taylor et al., 2024 [14]	Endogenous Expression Modification MANF	*C. elegans.*	MANF mutants vs. wild-type *C. elegans*	DA survival and motor function improvement.	To determine how MANF regulates autophagy and lysosome function to maintain proteostasis in *Caenorhabditis elegans*.
30. Yang et al., 2014 [88]	Recombinant MANF administration	Species: Male Sprague Dawley rats (6 to 8 weeks old, weighing 150–200 g). Model: Focal cerebral ischemia induced by MCAO (Middle Cerebral Artery Occlusion) to simulate stroke in rats.	MANF treatment vs. ischemic injury controls	Motor function improvement.	To assess whether MANF prevents neuron loss by inhibiting apoptosis induced by cerebral ischemia.
31. Stepanova et al., 2023 [85]	Recombinant Protein Administration (CDNF infusion)	N171-82Q transgenic mouse model of HD.	CDNF infusion vs. vehicle in HD model	Motor function and behavioural improvement.	To evaluate whether chronic CDNF infusion improves behavioural deficits in the N171-82Q mouse model of HD.
32. Jaumotte et al., 2021 [74]	Recombinant CDNF in cell culture	Species: Postnatal rat (P0) mesencephalic cultures. Model: Cultures from SN and ventral tegmental area (VTA).	CDNF and N4 treated vs. MPP+ toxin-exposed neurons	DA survival improvement.	To assess whether combining CDNF and neurturin variant N4 protects rat mesencephalic dopamine neurons from MPP^+ toxicity in vitro.

33.Voutilainen et al., 2017 [96]	Combination Therapy (CDNF + Other Treatment Methods)	Species: Male Wistar rats (250–280 g) Model: 6-hydroxydopamine (6-OHDA)-lesioned hemiparkinsonian rats	Combined CDNF and GDNF treatment vs. individual or no treatment	DA survival and motor function improvement.	To determine if co-administration of CDNF and GDNF produces additive neurorestorative effects in hemiparkinsonian rats, suggesting distinct mechanisms of action.
34. Zhang, et al., 2023 [47]	Recombinant Protein Administration (MANF injection)	Species: Sprague-Dawley rats Model: 6-hydroxydopamine (6-OHDA)-induced PD.	MANF-treated neuroinflammation model vs. untreated controls	DA survival and motor function improvement.	To determine whether elevated MANF expression prevents neuroinflammation-induced dopaminergic neurodegeneration in a 6-OHDA rat model of PD by modulating microglial activation and the AKT/GSK3β–Nrf2 signaling pathway.
35. Zhang et al., 2022 [39]	Recombinant MANF in in vitro cell cultures	Species: Sprague-Dawley rats, SH-SY5Y cells Model: Rotenone-induced PD model	MANF-treatment vs. α-synuclein accumulation controls	DA survival and motor function improvement.	To evaluate if MANF reduces α-synuclein accumulation by activating autophagy in a PD model.
36. Airavaara et al., 2012 [64]	Recombinant CDNF in in vitro cell cultures	Species: C57/Bl6 mice Model: MPTP-induced PD model	CDNF-treated MPTP mouse model vs. untreated controls	DA survival and motor function improvement.	To determine whether striatal CDNF administration protects and restores the nigrostriatal dopamine system, improving motor function in MPTP-treated mice.
37. Gao et al., 2024 [97]	Recombinant Protein Administration (MANF injection)	Species: C57BL/6 neonatal mice (both male and female) Model: Sevoflurane-induced cognitive impairment model	MANF-treated neonatal mice vs. controls	Motor function improvement.	To assess whether exogenous MANF administration mitigates sevoflurane-induced cognitive impairment in neonatal mice by modulating microglial activation and polarization.

38. Liu et al., 2018 [48]	Recombinant MANF treatment, cell culture	Species: C57BL/6 mice Model: MPTP-induced PD model	MANF treatment in MPP+/MPTP models vs. untreated controls	DA survival and motor function improvement.	To determine if MANF protects against MPP+/MPTP-induced PD by enhancing mitochondrial function and reducing oxidative stress.
39. Silva et al., 2021 [55]	Voluntary exercise increasing CDNF expression	Species: Swiss mice, male Model: 6-OHDA-induced PD model (bilateral injection)	PD mouse model with exercise-induced CDNF increase vs. sedentary controls	DA survival and motor function improvement.	To determine if physical exercise enhances tyrosine hydroxylase and CDNF levels in the spinal cord of a PD mouse model.
40. Wang et al., 2017 [65]	Gene therapy: AAV-CDNF delivery	Species: Wistar rats Model: Methamphetamine-induced neurotoxicity model	AAV-8-CDNF treated rats vs. vehicle controls under methamphetamine toxicity		To assess if AAV8-CDNF gene delivery protects against methamphetamine-induced dopaminergic neurotoxicity in rats.
41. Hartman et al., 2019 [84]	Endogenous Expression Modification (Knockout)	Species: Caenorhabditis elegans Model: manf-1 (tm3603) mutant (MANF-deficient) vs wild-type (N2)	MANF knockout vs. wild-type *C. elegans* under stress exposure	DA survival improvement.	To assess if deletion of MANF in *C. elegans* abolishes the early larval stress response to tunicamycin and *Pseudomonas aeruginosa*.

42. Albert et al., 2021 [102]	Recombinant Protein Administration (CDNF injection)	Species: Adult male Wistar rats Model: Quinolinic acid (QA)-induced neurotoxicity model of HD.	CDNF-treated α-synuclein PFF mice vs vehicle-treated α-synuclein PFF controls.	Motor function and behavioural improvement.	To assess whether CDNF treatment reduced α-synuclein aggregation, preserved dopaminergic neurons, and improved behavioral outcomes in a mouse model of PD.
43. Olivares-García et al., 2025 [56]	Forced exercise increasing CDNF expression	Species: CD1 male mice Model: Forced exercise in young male mice	Exercise-treated young mice vs. sedentary controls	Motor function improvement.	To assess if early-life exercise prevents adult anergia from dopamine loss via changes in CDNF and DARPP-32 signaling.
44. Caglayan et al., 2023 [62]	Combination Therapy (CDNF + Other Treatment Methods)	Species: C57BL6/J mice. Model: post-ischemic stroke model	CDNF/MANF treatment post-ischemia vs. untreated controls	Motor function and behavioural improvement.	To assess whether CDNF and MANF promote recovery, brain remodeling, and axonal plasticity after stroke in mice.
45. Kulesskaya et al., 2023 [42]	Peptidomimetic CDNF analog (HER-096)	Species: young male Sprague Dawley rats and young adult male CD-1 mice Model: PD	CDNF-derived peptide treatment vs. untreated synucleinopathy model	DA survival, motor function and behavioural improvement.	To determine whether the brain-penetrant CDNF peptidomimetic HER-096 protects dopaminergic neurons in a mouse synucleinopathy model of PD.
46. Wen et al., 2024 [94]	Endogenous MANF knockout in mouse	Species: C57BL/6J mice (male and female) Model: Neuron-specific MANF knockout (KO) mouse model	Neuron-specific MANF deficient mice vs. wild-type controls	Behavioural improvement.	To evaluate whether neuron-specific deletion of MANF alters alcohol-induced neurobehavioural deficits and ER stress in a sex-dependent manner.

47. Chen et al., 2020 [99]	Endogenous CDNF expression study	Species: Zebrafish (Danio rerio) Model: cdnf mutant zebrafish (CRISPR/Cas 9 knockout)	CDNF regulation in multiple neuronal subtypes vs. controls	DA survival and behavioural improvement.	To determine how CDNF regulates neurotransmitter circuits and behaviour by examining its effects on dopaminergic, GABAergic, and histaminergic neuron development and associated behavioural outcomes in zebrafish.
48. Mätlik et al., 2017 [98]	Recombinant Protein Administration (CDNF injection)	Species: Male Wistar rats Model: PD model (6-OHDA-induced).	Intrastriatal CDNF infusion vs. no infusion controls	DA survival improvement.	To assess whether intrastriatally infused CDNF is endocytosed and retrogradely transported to the SN.
49. Rafie et al., 2023 [57]	Exercise Intervention (Voluntary/Forced Exercise increasing endogenous MANF/CDNF)	Species: Male Wistar rats (8-10 weeks), Model: MPTP-induced PD model	Voluntary and forced exercise models in PD vs. no exercise	Motor function and behavioural improvement.	To compare how voluntary versus forced exercise affects cognitive function and neurotrophic factor (CDNF & BDNF) levels in a PD rat model.
50. Cordero-Llana et al., 2015 [100]	Combination Therapy (CDNF + Other Treatment Methods)	Species: Male Wistar rats (280–310g), Model: 6-OHDA-induced PD model	Combined intranigral CDNF/MANF overexpression vs. single gene overexpression	DA survival improvement, motor function, and behavioural improvement.	To determine whether combined intranigral overexpression of CDNF and MANF produces synergistic neuroprotective and functional benefits in the 6-OHDA rat model of PD.
51. Ren et al., 2013 [50]	Gene therapy: AAV2-CDNF delivery	Rats, 6-OHDA-lesioned model of PD.	AAV2-CDNF gene delivery vs. 6-OHDA lesion-only rat controls	DA survival improvement, motor function, and behavioural improvement.	To determine whether AAV2-mediated delivery of human CDNF to the striatum prevents degeneration of midbrain dopamine neurons in a 6-OHDA rat model.
52. Mei et al., 2015 [53]	Gene therapy: AAV-CDNF-expressing stem cells, Stem cell delivery of CDNF	Species: Female Sprague-Dawley rats Model: intrastriatal 6-OHDA lesion	CDNF-expressing bone marrow stromal cells vs. untreated controls	DA survival and motor function improvement.	To assess whether intrastriatal transplantation of CDNF-expressing bone marrow stromal cells protects dopaminergic neurons, restores tyrosine hydroxylase levels, and improves behaviour in a 6-OHDA rat model of PD.

53. Voutilainen et al., 2009 [19]	Recombinant Protein Administration (MANF injection)	Species: Adult male Wistar rats Model: intrastriatal 6-OHDA lesion model	MANF treatment vs. Parkinson's rat model controls	DA survival and motor function improvement.	To evaluate the neuroprotective and neurorestorative potential of MANF in a 6-OHDA rat model of PD.
54. Zhao et al., 2024 [41]	Endogenous MANF regulation in the ischemic model	Species: C57BL/6 mice Model: MCAO/R Species:BV-2 cells. Model: oxygen glucose deprivation/oxygenation (OGD/R)	MANF treatment vs. ischemia/reperfusion injury controls	Cellular function improvement.	To determine whether MANF alleviates cerebral ischemia/reperfusion injury in mice by regulating microglial polarization through the A20/NF-κB pathway.
55. Nam et al., 2024 [51]	Gene therapy: AAV-CDNF delivery	Species: Male C57BL/6 mice, 9–10 weeks old (~28 g) Model: acute MPTP lesion model	AAV--mediated CDNF gene transfer vs. MPTP mouse model controls	DA survival and motor function improvement.	To assess whether AAV-mediated delivery of CDNF protects dopamine neurons and reduces ER stress and inflammation in an acute MPTP mouse model of PD.
56. Liu et al., 2023 [58]	Recombinant CDNF protein Cell Culture Treatment (in vitro)	Species: Rat (PC12 cell line derived from rat adrenal pheochromocytoma) Model: 6-OHDA-lesiobed cell model	CDNF subdomain mutants vs. wild-type CDNF in PC12 cells	DA survival improvement.	To identify which CDNF subdomains (α1/α7) regulate its neuroprotective activity, using 6-OHDA-lesioned PC12 cells.
57. Lindahl et al., 2020 [60]	Endogenous CDNF knockout in mouse	Species: CDNF knockout mouse model (Cdnf−/−), Model: wild-type controls (C57BL/6J Rcc and ICR	CDNF-deficient mice vs. wild-type controls	DA survival and motor function improvement.	To determine the consequences of CDNF deficiency on enteric neuron integrity and dopaminergic function in mice.

		backgrounds)			
58. Zhou et al., 2025 [33]	Endogenous MANF overexpression	Species: In vitro: BV2 murine microglial cells (mouse origin) In vivo: Adult male C57BL/6 mice, 8 weeks old Model: In vitro: LPS-induced inflammatory stress and SNCA overexpression in BV2 cells In vivo: Rotenone-induced PD mouse model (3 mg/kg subcutaneous rotenone for 28 days)	MANF treatment vs. α-synuclein neuroinflammation controls	DA survival improvement.	To assess whether MANF inhibits neuroinflammation by promoting autophagy-mediated clearance of α-synuclein.
59. Mätlik et al., 2018 [46]	Recombinant Protein Administration (MANF injection)	species: Male Sprague-Dawley rats (200–320 g) Model: dMCAo (distal middle cerebral artery occlusion) model of focal cerebral ischemia	Poststroke MANF delivery vs. vehicle-treated stroke controls	Motor function and behavioural improvement.	To determine if poststroke delivery of MANF enhances neurological recovery, brain repair, and functional recovery in a rat model of ischemic stroke.

60. Huotarinen et al., 2018 [103]	Combination of CDNF and Other treatment (deep brain stimulation (DBS)).	Species: Male Wistar rats (220-300 g), Model: 6-OHDA MFB PD model	CDNF + DBS combined vs. DBS alone in late-stage Parkinson's model	Motor function improvement.	To test whether combining CDNF with deep brain stimulation reduces neurological deficits in a late-stage Parkinson's rat model.
61. Airavaara et al., 2010 [63]	Endogenous Expression Modification (Overexpression via AAV)	Species: Adult male Sprague-Dawley rats (250-350 g Model: MCAO stroke	Widespread cortical MANF overexpression vs. controls	Motor function and behavioural improvement.	To assess whether AAV7-mediated cortical expression of MANF reduces ischemic brain injury and promotes functional recovery after stroke in rats.
62. Hao et al., 2017 [76]	Gene therapy: AAV9-MANF delivery	Species: Adult female Sprague-Dawley rats. Model: 6-OHDA-lesioned Parkinsonian rats.	Long-term AAV9-MANF gene transfer vs. untreated Parkinson's rats	DA survival improvement, motor function, and behavioural improvement.	To evaluate the long-term neuroprotective effects of AAV9-mediated MANF gene transfer in a rat model of PD.
63. Latge et al., 2015 [73]	Recombinant Protein Administration (CDNF injection)	Primary dopaminergic neuron cultures from E14 mouse mesencephalon, N2a cell cultures	Structural studies comparing wild-type CDNF vs. mutants	DA survival improvement.	To characterize the structure of full-length CDNF and test its ability to protect dopaminergic neurons from α-synuclein oligomer toxicity.
64. Li et al., 2019 [89]	Recombinant MANF protein injection	Species: adult male Sprague-Dawley rats Model: SAH model	MANF treatment vs. subarachnoid hemorrhage injury controls	Motor function improvement.	To determine if MANF protects against early brain injury after subarachnoid hemorrhage by activating Akt survival signaling and preserving the blood–brain barrier.
65. Lindholm et al., 2007 [44]	Recombinant CDNF protein injection	Species: Male Wistar rats (250–280 g) Model: , 6-OHDA-induced PD model	Novel CDNF treatment vs. untreated controls	DA survival and motor function.	To determine whether CDNF protects and rescues midbrain dopaminergic neurons, both before and after 6-OHDA lesion, in a rat model of PD.

66. Eesmaa et al., 2021 [79]	Endogenous MANF overexpression	Rat (embryonic midbrain DA neurons for in vitro experiments), PD rat model for in vivo	MANF treatment vs. GRP78 cofactor independent controls	DA survival improvement.	To determine whether MANF promotes neuronal survival during ER stress independently of its cofactor role with GRP78.
67. Li et al., 2022 [40]	Endogenous MANF overexpression in MPTP model	Species: Adult male C57BL/6 J mice Model: MPTP to induce PD. Species: SH-SY5Y cells and primary midbrain neurons from embryonic mice were also used for in vitro studies.	Dendrobine + MANF vs. saline in Parkinson's models	DA survival improvement and motor function improvement.	To evaluate whether dendrobine protects dopaminergic neurons from apoptosis in MPTP/MPP^+-induced PD models by upregulating MANF expression and suppressing endoplasmic reticulum (ER) stress.
68. Tian et al., 2021 [71]	Gene therapy: AAV2-CDNF delivery	Species: Rats (Sprague Dawley) Model: dopamine D2 receptor allosteric modulator (PAOPA) treatment model	D2 modulator effects on CDNF expression vs. controls	DA survival improvement.	To evaluate whether chronic administration of the D2 allosteric modulator PAOPA increases CDNF expression in brain regions associated with neuropsychiatric disorders.
69. Chalazonitis et al., 2020	Endogenous CDNF knockout in mouse	Species: Mice (C57BL/6J background) Model: Cdnf knockout (Cdnf−/−) mouse model	CDNF-deficient vs. wild-type mice for enteric nervous system studies	DA survival improvement.	To investigate the role of CDNF in enteric neuron development, maintenance, and gastrointestinal motility regulation in mice.
70. Zhang et al., 2023 [54]	Stem cell delivery of MANF	Species: Rats (Sprague Dawley)Model: MCAO model	MANF-modified BMSC treatment vs. untreated infarction controls	Motor function and behavioural improvement.	To evaluate whether MANF improves bone marrow stromal cell-mediated pyroptosis inhibition, reducing cerebral infarction injury.

71. Pakarinen et al., 2022 [32]	Recombinant CDNF and MANF protein injection	Species: Mice (C57BL/6JRccHsd, ICR background). Model: double knockout mice (Cdnf-/- :: Manf-/-)	CDNF/MANF tissue-specific regulation vs. controls	DA survival improvement.	To determine how CDNF and MANF differentially regulate ER stress responses across various tissues.
72. Palgi et al., 2008 [81]	Endogenous Overexpression or knockout of DmMANF	Species: *Drosophila* melanogaster (fruit Species: DmMANF maternal and zygotic null mutants	DmMANF mutants vs. wild-type flies	DA survival improvement.	To establish that DmMANF supports dopaminergic neuron survival and function in *Drosophila melanogaster*.
73. Villa-Cedillo et al., 2023 [75]	Combination Therapy (CDNF + Other Treatment Methods)	C57BL/6J male mice (8-week-old, 25 ± 2 g)	CDNF intrastriatal delivery vs. untreated Parkinson's model	DA survival improvement, motor function, and behavioural improvement.	To test whether CPP-mediated intrastriatal CDNF overexpression prevents motor and cognitive deficits in a PD model.
74. Singh et al., 2023 [35]	Combination Therapy (CDNF + Other Treatment Methods)	Species: C57BL/6 mice Model: PFF model and 6-OHDA PD model	Alpha-synuclein + 6-OHDA vs. combined treatment with CDNF	DA survival and motor function improvement.	To develop a combined α-synuclein and 6-OHDA PD mouse model and evaluate CDNF's neuroprotective effects.
75. Airavaara et al., 2009 [90]	Recombinant Protein Administration (MANF injection)	Species: Adult male Sprague-Dawley rats (250–350 g); Model: MCAo stroke model	CDNF treatment vs. ischemic injury controls	Motor function improvement.	To assess if MANF reduces ischemic brain damage and improves functional recovery post-stroke in rats.
76. Kaminskaya et al., 2023 [70]	Endogenous Expression Modification (Overexpression)	Adult male ASC (Antidepressant Sensitive Catalepsy) mice	Hippocampal CDNF overexpression vs. depressive-like behaviour mice	Behavioural improvement.	To examine whether hippocampal CDNF overexpression alters depressive-like behaviours in genetically susceptible mice.

77. Sun et al., 2017 [34]	Cell Culture Treatment (in vitro)	Species: Human-derived Model: SH-SY5Y human neuroblastoma cells	MANF treatment vs. untreated SHSY-5Y cells	DA survival improvement,	To determine if MANF protects SHSY-5Y cells from apoptosis by increasing HSP70 expression.
78. Zhang et al., 2017 [93]	Recombinant Protein Administration (MANF injection)	Species: SH-SY5Y human neuroblastoma cells Model: 6-OHDA in vitro model of PD	MANF treatment vs. 6-OHDA-induced cell damage controls		To investigate MANF's neuroprotection against 6-OHDA toxicity through modulation of ROS-AMPK/mTOR signaling and autophagy inhibition.
79. Renko et al., 2018 [77]	Recombinant MANF, CDNF (CHO cells), GDNF (E. coli produced)	Male Wistar rats, intact, freely moving	MANF treatment vs. untreated freely moving rats	DA survival improvement.	To assess if MANF increases stimulus-induced dopamine release in awake, freely moving rats.
80. Nadella et al., 2014 [67]	Gene therapy (hCDNF plasmid, NTS-polyplex delivery, non-viral vector)	Male Wistar rats, 6-OHDA unilateral lesion model of PD.	CDNF transfection vs. 6-OHDA neuroinflammation controls	DA survival improvement.	To evaluate whether transient human CDNF gene transfection attenuates 6-OHDA-induced neuroinflammation in rat SN.