
Title

From Inhalation to Neurodegeneration: Air Pollution as a Modifiable Risk Factor for Alzheimer's Disease

Abstract

Air pollution, a growing concern for public health, has been linked to various respiratory and cardiovascular diseases. Emerging evidence also suggests a link between exposure to air pollutants and neurodegenerative diseases, particularly Alzheimer's disease (AD). This review explores the composition and sources of air pollutants, including particulate matter, gases, persistent organic pollutants, and heavy metals. The pathophysiology of AD is briefly discussed, highlighting the role of beta-amyloid plaques, neurofibrillary tangles, and genetic factors. This article also examines how air pollutants reach the brain and exert their detrimental effects, delving into the neurotoxicity of air pollutants. The molecular mechanisms linking air pollution to neurodegeneration are explored in detail, focusing on oxidative stress, neuroinflammation, and protein aggregation. Preclinical studies, including in vitro experiments and animal models, provide evidence for the direct effects of pollutants on neuronal cells, glial cells, and the blood-brain barrier. Epidemiological studies have reported associations between exposure to air pollution and an increased risk of AD and cognitive decline. The growing body of evidence supporting air pollution as a modifiable risk factor for AD underscores the importance of considering environmental factors in the etiology and progression of neurodegenerative diseases, in the face of worsening global air quality. © 2024 by the authors.

Authors

Olloquequi J.; Díaz-Peña R.; Verdaguer E.; Ettcheto M.; Auladell C.; Camins A.

Author full names

Olloquequi, Jordi (35763297900); Díaz-Peña, Roberto (15077936900); Verdaguer, Ester (7003342744); Ettcheto, Miren (56572786800); Auladell, Carme (6603054905); Camins, Antoni (7004127650)

Author(s) ID

35763297900; 15077936900; 7003342744; 56572786800; 6603054905;
7004127650

Year

2024

Source title

International Journal of Molecular Sciences

Volume

25.0

Issue

13.0

Art. No.

6928.0

DOI

10.3390/ijms25136928

Link

<https://www.scopus.com/inward/record.uri?eid=2-s2.0-85198354075&doi=10.3390%2fijms25136928&partnerID=40&md5=366580613239407f7e95073d02244622>

Affiliations

Department of Biochemistry and Physiology, Physiology Section, Faculty of Pharmacy and Food Science, Universitat de Barcelona, Barcelona, 08028, Spain; Laboratory of Cellular and Molecular Pathology, Instituto de Ciencias Biomédicas, Facultad de Ciencias de la Salud, Universidad Autónoma de Chile, Talca, 3460000, Chile; Fundación Pública Galega de Medicina Xenómica, SERGAS, Grupo de Medicina Xenómica-USC, Instituto de Investigación Sanitaria de Santiago (IDIS), Santiago de Compostela, 15706, Spain; Department of Cellular Biology, Physiology and Immunology, Faculty of Biology, Universitat de Barcelona, Barcelona, 08028, Spain; Institute of Neuroscience, Universitat de Barcelona, Barcelona, 08028, Spain; Biomedical Research Networking Center in Neurodegenerative Diseases (CIBERNED), Madrid, 28031, Spain; Institut d'Investigació Sanitària Pere Virgili (IISPV), Reus, 43204, Spain; Department of Pharmacology, Toxicology and Therapeutic Chemistry, Faculty of Pharmacy and Food Science, Universitat de

Barcelona, Barcelona, 08028, Spain

Authors with affiliations

Olloquequi J., Department of Biochemistry and Physiology, Physiology Section, Faculty of Pharmacy and Food Science, Universitat de Barcelona, Barcelona, 08028, Spain, Laboratory of Cellular and Molecular Pathology, Instituto de Ciencias Biomédicas, Facultad de Ciencias de la Salud, Universidad Autónoma de Chile, Talca, 3460000, Chile; Díaz-Peña R., Laboratory of Cellular and Molecular Pathology, Instituto de Ciencias Biomédicas, Facultad de Ciencias de la Salud, Universidad Autónoma de Chile, Talca, 3460000, Chile, Fundación Pública Galega de Medicina Xenómica, SERGAS, Grupo de Medicina Xenómica-USC, Instituto de Investigación Sanitaria de Santiago (IDIS), Santiago de Compostela, 15706, Spain; Verdaguer E., Department of Cellular Biology, Physiology and Immunology, Faculty of Biology, Universitat de Barcelona, Barcelona, 08028, Spain, Institute of Neuroscience, Universitat de Barcelona, Barcelona, 08028, Spain, Biomedical Research Networking Center in Neurodegenerative Diseases (CIBERNED), Madrid, 28031, Spain; Ettcheto M., Institute of Neuroscience, Universitat de Barcelona, Barcelona, 08028, Spain, Biomedical Research Networking Center in Neurodegenerative Diseases (CIBERNED), Madrid, 28031, Spain, Institut d'Investigació Sanitària Pere Virgili (IISPV), Reus, 43204, Spain, Department of Pharmacology, Toxicology and Therapeutic Chemistry, Faculty of Pharmacy and Food Science, Universitat de Barcelona, Barcelona, 08028, Spain; Auladell C., Department of Cellular Biology, Physiology and Immunology, Faculty of Biology, Universitat de Barcelona, Barcelona, 08028, Spain, Institute of Neuroscience, Universitat de Barcelona, Barcelona, 08028, Spain, Biomedical Research Networking Center in Neurodegenerative Diseases (CIBERNED), Madrid, 28031, Spain; Camins A., Institute of Neuroscience, Universitat de Barcelona, Barcelona, 08028, Spain, Biomedical

Research Networking Center in Neurodegenerative Diseases (CIBERNED), Madrid, 28031, Spain, Institut d'Investigació Sanitària Pere Virgili (IISPV), Reus, 43204, Spain, Department of Pharmacology, Toxicology and Therapeutic Chemistry, Faculty of Pharmacy and Food Science, Universitat de Barcelona, Barcelona, 08028, Spain

Author Keywords

Alzheimer's disease; dementia; neurodegeneration; neuroinflammation; neurotoxicity; oxidative stress; particulate matter

Index Keywords

Air Pollutants; Air Pollution; Alzheimer Disease; Animals; Brain; Environmental Exposure; Humans; Neurodegenerative Diseases; Oxidative Stress; Particulate Matter; Risk Factors; heavy metal; air pollutant; air pollution; air quality; Alzheimer disease; animal model; blood brain barrier; cardiovascular disease; cognitive defect; degenerative disease; dementia; drug toxicity; environmental factor; etiology; glia cell; human; in vitro study; inhalation; nerve degeneration; nervous system inflammation; neurofibrillary tangle; neurotoxicity; nonhuman; oxidative stress; particulate matter; pathophysiology; persistent organic pollutant; protein aggregation; review; risk factor; adverse event; air pollutant; animal; brain; environmental exposure; metabolism; oxidative stress; particulate matter; pathology; risk factor; toxicity

Chemicals/CAS

Air Pollutants, ; Particulate Matter,

References

Manisalidis I., Stavropoulou E., Stavropoulos A., Bezirtzoglou E., Environmental and Health Impacts of Air Pollution: A Review, *Front. Public Health*, 8, (2020); W.H.O. Air Pollution; Cohen A.J., Brauer M., Burnett R., Anderson H.R., Frostad J., Estep K., Balakrishnan K., Brunekreef B., Dandona L., Dandona R., Et al., Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: An analysis of data from the Global Burden of Diseases Study 2015, *Lancet*, 389, pp. 1907-1918, (2017); Hunt A., Ferguson J., Hurley F., Searl A., Social Costs of Morbidity Impacts of Air Pollution, *OECD Environment Working Papers*, (2016); Boogaard H., Walker K., Cohen A.J., Air pollution: The emergence of a major global health risk factor, *Int. Health*, 11, pp. 417-421, (2019); Dugger B.N., Dickson D.W., Pathology of Neurodegenerative Diseases, *Cold Spring Harb. Perspect. Biol*, 9, (2017); Gitler A.D., Dhillon P., Shorter J., Neurodegenerative disease: Models, mechanisms, and a new hope, *Dis. Model. Mech*, 10, pp. 499-502, (2017); Hou Y., Dan X., Babbar M., Wei Y., Hasselbalch S.G., Croteau D.L., Bohr V.A., Ageing as a risk factor for neurodegenerative disease, *Nat. Rev. Neurol*, 15, pp. 565-581, (2019); Mensah-Kane P., Sumien N., The potential of hyperbaric oxygen as a therapy for neurodegenerative diseases, *Geroscience*, 45, pp. 747-756, (2023); Gammon K., Neurodegenerative disease: Brain windfall, *Nature*, 515, pp. 299-300, (2014); Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: An analysis for the Global Burden of Disease Study 2019, *Lancet Public Health*, 7, pp. e105-e125, (2022); 2023 Alzheimer's disease facts and figures, *Alzheimer's Dement*, 19, pp. 1598-1695, (2023); Khreis H., Bredell C., Wai Fung K., Hong L., Szybka M., Phillips V., Abbas A., Lim Y.H., Jovanovic Andersen Z., Woodcock J., Et al., Impact of long-term air pollution exposure on incidence of neurodegenerative diseases: A protocol for a systematic review and exposure-response meta-analysis, *Environ. Int*, 170, (2022); Pipal A.S., Dubey S.,

Taneja A., Health Risk Assessment and Management of Air Pollutants, Air Pollution and Environmental Health, VII, pp. 209-232, (2020); Singh N., Air Pollution Exposure Studies Related to Human Health, Air Pollution and Environmental Health, VII, pp. 141-177, (2020); Taneja A., Saini R., Masih A., Indoor air quality of houses located in the urban environment of Agra, India, Ann. N. Y. Acad. Sci, 1140, pp. 228-245, (2008); W.H.O. Household Air Pollution; Olloquequi J., Silva O.R., Biomass smoke as a risk factor for chronic obstructive pulmonary disease: Effects on innate immunity, Innate Immun, 22, pp. 373-381, (2016); Leech J.A., Nelson W.C., Burnett R.T., Aaron S., Raizenne M.E., It's about time: A comparison of Canadian and American time-activity patterns, J. Expo. Anal. Environ. Epidemiol, 12, pp. 427-432, (2002); Falkowska L., Environmental characteristics of gaseous pollutants and related adverse health effects, Synergic Influence of Gaseous Particulate, and Biological Pollutants on Human Health, pp. 2-28, (2015); Mannucci P.M., Harari S., Martinelli I., Franchini M., Effects on health of air pollution: A narrative review, Intern. Emerg. Med, 10, pp. 657-662, (2015); Jackson A.V., Sources of Air Pollution, Handbook of Atmospheric Science, pp. 124-155, (2003); Tang Y., Sources of underground CO: Crushing and ambient temperature oxidation of coal, J. Loss Prev. Process Ind, 38, pp. 50-57, (2015); Chiang P.-C., Gao X., SO_x Control, Air Pollution Control and Design, pp. 7-47, (2022); Lin C.K., Lin R.T., Chen P.C., Wang P., De Marcellis-Warin N., Zigler C., Christiani D.C., A Global Perspective on Sulfur Oxide Controls in Coal-Fired Power Plants and Cardiovascular Disease, Sci. Rep, 8, (2018); Kleinman L.I., The dependence of tropospheric ozone production rate on ozone precursors, Atmos. Environ, 39, pp. 575-586, (2005); Lee D.S., Kohler I., Grobler E., Rohrer F., Sausen R., Gallardo-Klenner L., Olivier J.G.J., Dentener F.J., Bouwman A.F., Estimations of global no_x emissions and their uncertainties, Atmos. Environ, 31, pp. 1735-1749, (1997); Saunio M., Stavert A.R., Poulter B., Bousquet P., Canadell J.G., Jackson R.B., Raymond P.A., Dlugokencky E.J., Houweling S., Patra P.K., The global methane budget 2000–2017, Earth Syst. Sci. Data Discuss, 2019, pp. 1-136, (2019);

Zhang J.J., Wei Y., Fang Z., Ozone Pollution: A Major Health Hazard Worldwide, *Front. Immunol*, 10, (2019); Scheringer M., Stempel S., Hukari S., Ng C.A., Blepp M., Hungerbuhler K., How many persistent organic pollutants should we expect?, *Atmos. Pollut. Res*, 3, pp. 383-391, (2012); Liu C., Hou H.S., Physical exercise and persistent organic pollutants, *Heliyon*, 9, (2023); Maring T., Kumar S., Jha A.K., Kumar N., Pandey S.P., Airborne Particulate Matter and Associated Heavy Metals: A Review, *Macromol. Symp*, 407, (2023); Martin-Cruz Y., Gomez-Losada A., Risk Assessment and Source Apportionment of Metals on Atmospheric Particulate Matter in a Suburban Background Area of Gran Canaria (Spain), *Int. J. Environ. Res. Public Health*, 20, (2023); Hamanaka R.B., Mutlu G.M., Particulate Matter Air Pollution: Effects on the Cardiovascular System, *Front. Endocrinol*, 9, (2018); Harrison R.M., Shi J.P., Shuhua X., Khan A., Mark D., Kinnersley R., Yin J., Measurement of Number, Mass and Size Distribution of Particles in the Atmosphere, *Philos. Trans. Math. Phys. Eng. Sci*, 358, pp. 2567-2580, (2000); Harrison R.M., Airborne particulate matter. *Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering, Sciences*, 378, (2020); Oberdorster G., Utell M.J., Ultrafine particles in the urban air: To the respiratory tract--and beyond?, *Environ. Health Perspect*, 110, pp. A440-A441, (2002); Calderon-Garciduenas L., Azzarelli B., Acuna H., Garcia R., Gambling T.M., Osnaya N., Monroy S., Tizapantzi M.D.R., Carson J.L., Villarreal-Calderon A., Et al., Air pollution and brain damage, *Toxicol. Pathol*, 30, pp. 373-389, (2002); Calderon-Garciduenas L., Maronpot R.R., Torres-Jardon R., Henriquez-Roldan C., Schoonhoven R., Acuna-Ayala H., Villarreal-Calderon A., Nakamura J., Fernando R., Reed W., Et al., DNA damage in nasal and brain tissues of canines exposed to air pollutants is associated with evidence of chronic brain inflammation and neurodegeneration, *Toxicol. Pathol*, 31, pp. 524-538, (2003); Zou Y.M., Lu D., Liu L.P., Zhang H.H., Zhou Y.Y., Olfactory dysfunction in Alzheimer's disease, *Neuropsychiatr. Dis. Treat*, 12, pp. 869-875, (2016); Genc S., Zadeoglulari Z., Fuss S.H., Genc K., The adverse effects of air pollution on the nervous system, *J.*

Toxicol, 2012, (2012); Oberdorster G., Elder A., Rinderknecht A., Nanoparticles and the brain: Cause for concern?, *J. Nanosci. Nanotechnol*, 9, pp. 4996-5007, (2009); Nemmar A., Hoet P.H., Vanquickenborne B., Dinsdale D., Thomeer M., Hoylaerts M.F., Vanbilloen H., Mortelmans L., Nemery B., Passage of inhaled particles into the blood circulation in humans, *Circulation*, 105, pp. 411-414, (2002); Nemmar A., Zia S., Subramaniyan D., Al-Amri I., Al Kindi M.A., Ali B.H., Interaction of diesel exhaust particles with human, rat and mouse erythrocytes in vitro, *Cell. Physiol. Biochem*, 29, pp. 163-170, (2012); Geiser M., Rothen-Rutishauser B., Kapp N., Schurch S., Kreyling W., Schulz H., Semmler M., Im Hof V., Heyder J., Gehr P., Ultrafine particles cross cellular membranes by nonphagocytic mechanisms in lungs and in cultured cells, *Environ. Health Perspect*, 113, pp. 1555-1560, (2005); Araujo J.A., Nel A.E., Particulate matter and atherosclerosis: Role of particle size, composition and oxidative stress, *Part. Fibre Toxicol*, 6, (2009); Oberdorster G., Oberdorster E., Oberdorster J., Nanotoxicology: An emerging discipline evolving from studies of ultrafine particles, *Environ. Health Perspect*, 113, pp. 823-839, (2005); Yarns B.C., Holiday K.A., Carlson D.M., Cosgrove C.K., Melrose R.J., Pathophysiology of Alzheimer's Disease, *Psychiatr. Clin. N. Am*, 45, pp. 663-676, (2022); Zhang Y., Chen H., Li R., Sterling K., Song W., Amyloid β -based therapy for Alzheimer's disease: Challenges, successes and future, *Signal Transduct. Target. Ther*, 8, (2023); Otero-Garcia M., Mahajani S.U., Wakhloo D., Tang W., Xue Y.-Q., Morabito S., Pan J., Oberhauser J., Madira A.E., Shakouri T., Et al., Molecular signatures underlying neurofibrillary tangle susceptibility in Alzheimer's disease, *Neuron*, 110, pp. 2929-2948.e8, (2022); Hampel H., Hardy J., Blennow K., Chen C., Perry G., Kim S.H., Villemagne V.L., Aisen P., Vendruscolo M., Iwatsubo T., Et al., The Amyloid- β Pathway in Alzheimer's Disease, *Mol. Psychiatry*, 26, pp. 5481-5503, (2021); Pfundstein G., Nikonenko A.G., Sytnyk V., Amyloid precursor protein (APP) and amyloid β ($A\beta$) interact with cell adhesion molecules: Implications in Alzheimer's disease and normal physiology, *Front. Cell Dev. Biol*, 10, (2022); Roselli S., Satir

T.M., Camacho R., Fruhwurth S., Bergstrom P., Zetterberg H., Agholme L., APP-BACE1 Interaction and Intracellular Localization Regulate A β Production in iPSC-Derived Cortical Neurons, *Cell. Mol. Neurobiol*, 43, pp. 3653-3668, (2023); Rawat P., Sehar U., Bisht J., Selman A., Culberson J., Reddy P.H., Phosphorylated Tau in Alzheimer's Disease and Other Tauopathies, *Int. J. Mol. Sci*, 23, (2022); Yamazaki Y., Zhao N., Caulfield T.R., Liu C.C., Bu G., Apolipoprotein E and Alzheimer disease: Pathobiology and targeting strategies, *Nat. Rev. Neurol*, 15, pp. 501-518, (2019); Andrade-Guerrero J., Santiago-Balmaseda A., Jeronimo-Aguilar P., Vargas-Rodriguez I., Cadena-Suarez A.R., Sanchez-Garibay C., Pozo-Molina G., Mendez-Catala C.F., Cardenas-Aguayo M.D., Diaz-Cintra S., Et al., Alzheimer's Disease: An Updated Overview of Its Genetics, *Int. J. Mol. Sci*, 24, (2023); Plachez C., Tsytsarev V., Zhao S., Erzurumlu R.S., Amyloid Deposition and Dendritic Complexity of Corticocortical Projection Cells in Five Familial Alzheimer's Disease Mouse, *Neuroscience*, 512, pp. 85-98, (2023); Yang Z., Zou Y., Wang L., Neurotransmitters in Prevention and Treatment of Alzheimer's Disease, *Int. J. Mol. Sci*, 24, (2023); Govindpani K., McNamara L.G., Smith N.R., Vinnakota C., Waldvogel H.J., Faull R.L., Kwakowsky A., Vascular Dysfunction in Alzheimer's Disease: A Prelude to the Pathological Process or a Consequence of It?, *J. Clin. Med*, 8, (2019); Ionescu-Tucker A., Cotman C.W., Emerging roles of oxidative stress in brain aging and Alzheimer's disease, *Neurobiol. Aging*, 107, pp. 86-95, (2021); Thakur S., Dhapola R., Sarma P., Medhi B., Reddy D.H., Neuroinflammation in Alzheimer's Disease: Current Progress in Molecular Signaling and Therapeutics, *Inflammation*, 46, pp. 1-17, (2023); Das N., Raymick J., Sarkar S., Role of metals in Alzheimer's disease, *Metab. Brain Dis*, 36, pp. 1627-1639, (2021); Kilian J., Kitazawa M., The emerging risk of exposure to air pollution on cognitive decline and Alzheimer's disease—Evidence from epidemiological and animal studies, *Biomed. J*, 41, pp. 141-162, (2018); Peters R., Ee N., Peters J., Booth A., Mudway I., Anstey K.J., Air Pollution and Dementia: A Systematic Review, *J. Alzheimer's Dis*, 70, pp. S145-S163, (2019); Clifford A., Lang

L., Chen R., Anstey K.J., Seaton A., Exposure to air pollution and cognitive functioning across the life course--A systematic literature review, *Environ. Res*, 147, pp. 383-398, (2016); Fu P., Yung K.K.L., Air Pollution and Alzheimer's Disease: A Systematic Review and Meta-Analysis, *J. Alzheimer's Dis*, 77, pp. 701-714, (2020); Hahad O., Lelieveld J., Birklein F., Lieb K., Daiber A., Munzel T., Ambient Air Pollution Increases the Risk of Cerebrovascular and Neuropsychiatric Disorders through Induction of Inflammation and Oxidative Stress, *Int. J. Mol. Sci*, 21, (2020); Lardelli M., An Alternative View of Familial Alzheimer's Disease Genetics, *J. Alzheimer's Dis*, 96, pp. 13-39, (2023); Halliwell B., Gutteridge J.M.C., *Free Radicals in Biology and Medicine*, (2015); Moulton P.V., Yang W., Air Pollution, Oxidative Stress, and Alzheimer's Disease, *J. Environ. Public Health*, 2012, (2012); Poon H.F., Calabrese V., Scapagnini G., Butterfield D.A., Free radicals and brain aging, *Clin. Geriatr. Med*, 20, pp. 329-359, (2004); Migliore L., Coppede F., Environmental-induced oxidative stress in neurodegenerative disorders and aging, *Mutat. Res*, 674, pp. 73-84, (2009); Sharma C., Kim S.R., Linking Oxidative Stress and Proteinopathy in Alzheimer's Disease, *Antioxidants*, 10, (2021); Ferre-Gonzalez L., Pena-Bautista C., Baquero M., Chafer-Pericas C., Assessment of Lipid Peroxidation in Alzheimer's Disease Differential Diagnosis and Prognosis, *Antioxidants*, 11, (2022); Kim G.H., Kim J.E., Rhie S.J., Yoon S., The Role of Oxidative Stress in Neurodegenerative Diseases, *Exp. Neurobiol*, 24, pp. 325-340, (2015); Ashok A., Andrabi S.S., Mansoor S., Kuang Y., Kwon B.K., Labhassetwar V., Antioxidant Therapy in Oxidative Stress-Induced Neurodegenerative Diseases: Role of Nanoparticle-Based Drug Delivery Systems in Clinical Translation, *Antioxidants*, 11, (2022); Kamat P.K., Kalani A., Rai S., Swarnkar S., Tota S., Nath C., Tyagi N., Mechanism of Oxidative Stress and Synapse Dysfunction in the Pathogenesis of Alzheimer's Disease: Understanding the Therapeutics Strategies, *Mol. Neurobiol*, 53, pp. 648-661, (2016); Pardillo-Diaz R., Perez-Garcia P., Castro C., Nunez-Abades P., Carrascal L., Oxidative Stress as a Potential Mechanism Underlying Membrane Hyperexcitability in

Neurodegenerative Diseases, *Antioxidants*, 11, (2022); Cory-Slechta D.A., Merrill A., Sobolewski M., Air Pollution-Related Neurotoxicity Across the Life Span, *Annu. Rev. Pharmacol. Toxicol.*, 63, pp. 143-163, (2023); Mezzaroba L., Alfieri D.F., Colado Simao A.N., Vissoci Reiche E.M., The role of zinc, copper, manganese and iron in neurodegenerative diseases, *Neurotoxicology*, 74, pp. 230-241, (2019); Masaldan S., Bush A.I., Devos D., Rolland A.S., Moreau C., Striking while the iron is hot: Iron metabolism and ferroptosis in neurodegeneration, *Free. Radic. Biol. Med.*, 133, pp. 221-233, (2019); Numan M.S., Brown J.P., Michou L., Impact of air pollutants on oxidative stress in common autophagy-mediated aging diseases, *Int. J. Environ. Res. Public Health*, 12, pp. 2289-2305, (2015); Zhang X., Staimer N., Gillen D.L., Tjoa T., Schauer J.J., Shafer M.M., Hasheminassab S., Pakbin P., Vaziri N.D., Sioutas C., Et al., Associations of oxidative stress and inflammatory biomarkers with chemically-characterized air pollutant exposures in an elderly cohort, *Environ. Res.*, 150, pp. 306-319, (2016); Valdez J.M., Johnstone A.F.M., Richards J.E., Schmid J.E., Royland J.E., Kodavanti P.R.S., Interaction of Diet and Ozone Exposure on Oxidative Stress Parameters within Specific Brain Regions of Male Brown Norway Rats, *Int. J. Mol. Sci.*, 20, (2018); Calabro V., Garces M., Caceres L., Magnani N.D., Marchini T., Freire A., Vico T., Martinefski M., Vanasco V., Tripodi V., Et al., Urban air pollution induces alterations in redox metabolism and mitochondrial dysfunction in mice brain cortex, *Arch. Biochem. Biophys.*, 704, (2021); Kim J.Y., Kim J.H., Kim Y.D., Seo J.H., High Vulnerability of Oligodendrocytes to Oxidative Stress Induced by Ultrafine Urban Particles, *Antioxidants*, 10, (2020); Lin C.H., Nicol C.J.B., Wan C., Chen S.J., Huang R.N., Chiang M.C., Exposure to PM(2.5) induces neurotoxicity, mitochondrial dysfunction, oxidative stress and inflammation in human SH-SY5Y neuronal cells, *Neurotoxicology*, 88, pp. 25-35, (2022); Fagundes L.S., Fleck Ada S., Zanchi A.C., Saldiva P.H., Rhoden C.R., Direct contact with particulate matter increases oxidative stress in different brain structures, *Inhal. Toxicol.*, 27, pp. 462-467, (2015); Kim J.Y., Hong S., Bolormaa O., Seo J.H., Eom S.Y., Kim Y.D., Kim H., Effects of diesel exhaust

particles and urban particles on brain endothelial cells, *Toxicol Res*, 38, pp. 91-98, (2022); Alkhalifa A.E., Al-Ghraiyyah N.F., Odum J., Shunnarah J.G., Austin N., Kaddoumi A., Blood-Brain Barrier Breakdown in Alzheimer's Disease: Mechanisms and Targeted Strategies, *Int. J. Mol. Sci*, 24, (2023); Bernardi R.B., Zanchi A.C.T., Damaceno-Rodrigues N.R., Veras M.M., Saldiva P.H.N., Barros H.M.T., Rhoden C.R., The impact of chronic exposure to air pollution over oxidative stress parameters and brain histology, *Environ. Sci. Pollut. Res. Int*, 28, pp. 47407-47417, (2021); Milani C., Farina F., Botto L., Massimino L., Lonati E., Donzelli E., Ballarini E., Crippa L., Marmiroli P., Bulbarelli A., Et al., Systemic Exposure to Air Pollution Induces Oxidative Stress and Inflammation in Mouse Brain, Contributing to Neurodegeneration Onset, *Int. J. Mol. Sci*, 21, (2020); Kodavanti P.R.S., Valdez M., Richards J.E., Agina-Obu D.I., Phillips P.M., Jarema K.A., Kodavanti U.P., Ozone-induced changes in oxidative stress parameters in brain regions of adult, middle-age, and senescent Brown Norway rats, *Toxicol. Appl. Pharmacol*, 410, (2021); Velazquez-Perez R., Rodriguez-Martinez E., Valdes-Fuentes M., Gelista-Herrera N., Gomez-Crisostomo N., Rivas-Arancibia S., Oxidative Stress Caused by Ozone Exposure Induces Changes in P2X7 Receptors, Neuroinflammation, and Neurodegeneration in the Rat Hippocampus, *Oxid. Med. Cell. Longev*, 2021, (2021); Rivas-Arancibia S., Guevara-Guzman R., Lopez-Vidal Y., Rodriguez-Martinez E., Zanardo-Gomes M., Angoa-Perez M., Raisman-Vozari R., Oxidative stress caused by ozone exposure induces loss of brain repair in the hippocampus of adult rats, *Toxicol. Sci*, 113, pp. 187-197, (2010); Guxens M., Lubczynska M.J., Perez-Crespo L., Muetzel R.L., El Marroun H., Basagana X., Hoek G., Tiemeier H., Associations of Air Pollution on the Brain in Children: A Brain Imaging Study, *Res. Rep. Health Eff. Inst*, 2022, (2022); Shabani K., Hassan B.A., The brain on time: Links between development and neurodegeneration, *Development*, 150, (2023); DiSabato D.J., Quan N., Godbout J.P., Neuroinflammation: The devil is in the details, *J. Neurochem*, 139, pp. 136-153, (2016); Norden D.M., Trojanowski P.J.,

Villanueva E., Navarro E., Godbout J.P., Sequential activation of microglia and astrocyte cytokine expression precedes increased Iba-1 or GFAP immunoreactivity following systemic immune challenge, *Glia*, 64, pp. 300-316, (2016); Hensley K., Neuroinflammation in Alzheimer's disease: Mechanisms, pathologic consequences, and potential for therapeutic manipulation, *J. Alzheimer's Dis*, 21, pp. 1-14, (2010); Sun Y., Koyama Y., Shimada S., Inflammation from Peripheral Organs to the Brain: How Does Systemic Inflammation Cause Neuroinflammation?, *Front. Aging Neurosci*, 14, (2022); Heneka M.T., Carson M.J., El Khoury J., Landreth G.E., Brosseron F., Feinstein D.L., Jacobs A.H., Wyss-Coray T., Vitorica J., Ransohoff R.M., Et al., Neuroinflammation in Alzheimer's disease, *Lancet Neurol*, 14, pp. 388-405, (2015); Onyango I.G., Jauregui G.V., Carna M., Bennett J.P., Stokin G.B., Neuroinflammation in Alzheimer's Disease, *Biomedicines*, 9, (2021); Lyra e Silva N.M., Goncalves R.A., Pascoal T.A., Lima-Filho R.A.S., Resende E., Vieira E.L.M., Teixeira A.L., de Souza L.C., Peny J.A., Fortuna J.T.S., Et al., Pro-inflammatory interleukin-6 signaling links cognitive impairments and peripheral metabolic alterations in Alzheimer's disease, *Transl. Psychiatry*, 11, (2021); Plantone D., Pardini M., Righi D., Manco C., Colombo B.M., De Stefano N., The Role of TNF- α in Alzheimer's Disease: A Narrative Review, *Cells*, 13, (2023); Saito T., Saido T.C., Neuroinflammation in mouse models of Alzheimer's disease, *Clin. Exp. Neuroimmunol*, 9, pp. 211-218, (2018); Kiraly M., Foss J.F., Giordano T., Neuroinflammation, its Role in Alzheimer's Disease and Therapeutic Strategie, *J. Prev. Alzheimer's Dis*, 10, pp. 686-698, (2023); Figueiredo-Pereira M.E., Rockwell P., Schmidt-Glenewinkel T., Serrano P., Neuroinflammation and J2 prostaglandins: Linking impairment of the ubiquitin-proteasome pathway and mitochondria to neurodegeneration, *Front. Mol. Neurosci*, 7, (2014); Liddelow S.A., Guttenplan K.A., Clarke L.E., Bennett F.C., Bohlen C.J., Schirmer L., Bennett M.L., Munch A.E., Chung W.S., Peterson T.C., Et al., Neurotoxic reactive astrocytes are induced by activated microglia, *Nature*, 541, pp. 481-487, (2017); Leng F., Edison P., Neuroinflammation and microglial activation in

Alzheimer disease: Where do we go from here?, *Nat. Rev. Neurol*, 17, pp. 157-172, (2021); Sama P., Long T.C., Hester S., Tajuba J., Parker J., Chen L.C., Veronesi B., The cellular and genomic response of an immortalized microglia cell line (BV2) to concentrated ambient particulate matter, *Inhal. Toxicol*, 19, pp. 1079-1087, (2007); Costa L.G., Cole T.B., Coburn J., Chang Y.C., Dao K., Roque P., Neurotoxicants are in the air: Convergence of human, animal, and in vitro studies on the effects of air pollution on the brain, *Biomed Res. Int*, 2014, (2014); Hartz A.M., Bauer B., Block M.L., Hong J.S., Miller D.S., Diesel exhaust particles induce oxidative stress, proinflammatory signaling, and P-glycoprotein up-regulation at the blood-brain barrier, *FASEB J*, 22, pp. 2723-2733, (2008); Seo S., Jang M., Kim H., Sung J.H., Choi N., Lee K., Kim H.N., Neuro-Glia-Vascular-on-a-Chip System to Assess Aggravated Neurodegeneration via Brain Endothelial Cells upon Exposure to Diesel Exhaust Particles, *Adv. Funct. Mater*, 33, (2023); Liu F., Huang Y., Zhang F., Chen Q., Wu B., Rui W., Zheng J.C., Ding W., Macrophages treated with particulate matter PM2.5 induce selective neurotoxicity through glutaminase-mediated glutamate generation, *J. Neurochem*, 134, pp. 315-326, (2015); Han B., Li X., Ai R.S., Deng S.Y., Ye Z.Q., Deng X., Ma W., Xiao S., Wang J.Z., Wang L.M., Et al., Atmospheric particulate matter aggravates cns demyelination through involvement of TLR-4/NF-kB signaling and microglial activation, *eLife*, 11, (2022); Campbell A., Oldham M., Becaria A., Bondy S.C., Meacher D., Sioutas C., Misra C., Mendez L.B., Kleinman M., Particulate matter in polluted air may increase biomarkers of inflammation in mouse brain, *Neurotoxicology*, 26, pp. 133-140, (2005); Kleinman M.T., Araujo J.A., Nel A., Sioutas C., Campbell A., Cong P.Q., Li H., Bondy S.C., Inhaled ultrafine particulate matter affects CNS inflammatory processes and may act via MAP kinase signaling pathways, *Toxicol. Lett*, 178, pp. 127-130, (2008); Bos I., De Boever P., Emmerechts J., Buekers J., Vanoirbeek J., Meeusen R., Van Poppel M., Nemery B., Nawrot T., Panis L.I., Changed gene expression in brains of mice exposed to traffic in a highway tunnel, *Inhal. Toxicol*, 24, pp. 676-686, (2012); Gerlofs-Nijland M.E., van Berlo D.,

Cassee F.R., Schins R.P., Wang K., Campbell A., Effect of prolonged exposure to diesel engine exhaust on proinflammatory markers in different regions of the rat brain, *Part. Fibre Toxicol*, 7, (2010); van Berlo D., Albrecht C., Knaapen A.M., Cassee F.R., Gerlofs-Nijland M.E., Kooter I.M., Palomero-Gallagher N., Bidmon H.J., van Schooten F.J., Krutmann J., Et al., Comparative evaluation of the effects of short-term inhalation exposure to diesel engine exhaust on rat lung and brain, *Arch. Toxicol*, 84, pp. 553-562, (2010); Yao G., Yue H., Yun Y., Sang N., Chronic SO₂ inhalation above environmental standard impairs neuronal behavior and represses glutamate receptor gene expression and memory-related kinase activation via neuroinflammation in rats, *Environ. Res*, 137, pp. 85-93, (2015); Calderon-Garciduenas L., Kavanaugh M., Block M., D'Angiulli A., Delgado-Chavez R., Torres-Jardon R., Gonzalez-Maciel A., Reynoso-Robles R., Osnaya N., Villarreal-Calderon R., Et al., Neuroinflammation, hyperphosphorylated tau, diffuse amyloid plaques, and down-regulation of the cellular prion protein in air pollution exposed children and young adults, *J. Alzheimer's Dis*, 28, pp. 93-107, (2012); Teleanu D.M., Niculescu A.G., Lungu I.I., Radu C.I., Vladacenco O., Roza E., Costachescu B., Grumezescu A.M., Teleanu R.I., An Overview of Oxidative Stress, Neuroinflammation, and Neurodegenerative Diseases, *Int. J. Mol. Sci*, 23, (2022); Abramov A.Y., Potapova E.V., Dremin V.V., Dunaev A.V., Interaction of Oxidative Stress and Misfolded Proteins in the Mechanism of Neurodegeneration, *Life*, 10, (2020); Liu Y., Nguyen M., Robert A., Meunier B., Metal Ions in Alzheimer's Disease: A Key Role or Not?, *Acc. Chem. Res*, 52, pp. 2026-2035, (2019); Bush A.I., Pettingell W.H., Multhaup G., d Paradis M., Vonsattel J.P., Gusella J.F., Beyreuther K., Masters C.L., Tanzi R.E., Rapid induction of Alzheimer A beta amyloid formation by zinc, *Science*, 265, pp. 1464-1467, (1994); Mantyh P.W., Ghilardi J.R., Rogers S., DeMaster E., Allen C.J., Stimson E.R., Maggio J.E., Aluminum, iron, and zinc ions promote aggregation of physiological concentrations of beta-amyloid peptide, *J. Neurochem*, 61, pp. 1171-1174, (1993); Tonnes E., Trushina E., Oxidative Stress, *Synaptic*

Dysfunction, and Alzheimer's Disease, *J. Alzheimer's Dis*, 57, pp. 1105-1121, (2017); Tamagno E., Guglielmotto M., Aragno M., Borghi R., Autelli R., Giliberto L., Muraca G., Danni O., Zhu X., Smith M.A., Et al., Oxidative stress activates a positive feedback between the gamma- and beta-secretase cleavages of the beta-amyloid precursor protein, *J. Neurochem*, 104, pp. 683-695, (2008); Muche A., Arendt T., Schliebs R., Oxidative stress affects processing of amyloid precursor protein in vascular endothelial cells, *PLoS ONE*, 12, (2017); Simpson D.S.A., Oliver P.L., ROS Generation in Microglia: Understanding Oxidative Stress and Inflammation in Neurodegenerative Disease, *Antioxidants*, 9, (2020); Devi S., Kim J.J., Singh A.P., Kumar S., Dubey A.K., Singh S.K., Singh R.S., Kumar V., Proteotoxicity: A Fatal Consequence of Environmental Pollutants-Induced Impairments in Protein Clearance Machinery, *J. Pers. Med*, 11, (2021); Tamas M.J., Fauvet B., Christen P., Goloubinoff P., Misfolding and aggregation of nascent proteins: A novel mode of toxic cadmium action in vivo, *Curr. Genet*, 64, pp. 177-181, (2018); Haghani A., Johnson R.G., Dalton H., Feinberg J.I., Lewis K.C., Ladd-Acosta C., Woodward N.C., Safi N., Jaffe A.E., Allayee H., Et al., Early developmental exposure to air pollution increases the risk of Alzheimers disease and amyloid production: Studies in mouse and *Caenorhabditis elegans*, *Alzheimer's Dement*, 16, (2020); Calderon-Garciduenas L., Solt A.C., Henriquez-Roldan C., Torres-Jardon R., Nuse B., Herritt L., Villarreal-Calderon R., Osnaya N., Stone I., Garcia R., Et al., Long-term air pollution exposure is associated with neuroinflammation, an altered innate immune response, disruption of the blood-brain barrier, ultrafine particulate deposition, and accumulation of amyloid beta-42 and alpha-synuclein in children and young adults, *Toxicol. Pathol*, 36, pp. 289-310, (2008); Kim S.H., Knight E.M., Saunders E.L., Cuevas A.K., Popovech M., Chen L.C., Gandy S., Rapid doubling of Alzheimer's amyloid- β 40 and 42 levels in brains of mice exposed to a nickel nanoparticle model of air pollution, *F1000Research*, 1, (2012); Sahu B., Mackos A.R., Floden A.M., Wold L.E., Combs C.K., Particulate Matter Exposure Exacerbates Amyloid- β Plaque

Deposition and Gliosis in APP/PS1 Mice, *J. Alzheimer's Dis*, 80, pp. 761-774, (2021); Motesaddi Zarandi S., Shahsavani A., Khodaghali F., Fakhri Y., Co-exposure to ambient PM_{2.5} plus gaseous pollutants increases amyloid β ₁₋₄₂ accumulation in the hippocampus of male and female rats, *Toxin Rev*, 40, pp. 300-309, (2021); Ku T., Chen M., Li B., Yun Y., Li G., Sang N., Synergistic effects of particulate matter (PM_{2.5}) and sulfur dioxide (SO₂) on neurodegeneration via the microRNA-mediated regulation of tau phosphorylation, *Toxicol. Res*, 6, pp. 7-16, (2017); Wenbin K., Xia Y., Wang J., Wang Y., Sulfur Dioxide Promotes the Formation of Amyloid Fibrils through Enhanced Secondary Nucleation: A Molecular Dynamics Study, *Acta Chim. Sin*, 74, (2016); Kaumbekova S., Torkmahalleh M.A., Shah D., Ammonium Sulfate and Ultrafine Particles Affect Early Onset of Alzheimer's Disease, *Chem. Eng. Trans*, 85, pp. 187-192, (2021); Kaumbekova S., Torkmahalleh M.A., Shah D., Ambient Benzo[a]pyrene's Effect on Kinetic Modulation of Amyloid Beta Peptide Aggregation: A Tentative Association between Ultrafine Particulate Matter and Alzheimer's Disease, *Toxics*, 10, (2022); Cacciottolo M., Morgan T.E., Saffari A.A., Shirmohammadi F., Forman H.J., Sioutas C., Finch C.E., Traffic-related air pollutants (TRAP-PM) promote neuronal amyloidogenesis through oxidative damage to lipid rafts, *Free. Radic. Biol. Med*, 147, pp. 242-251, (2020); Greve H.J., Dunbar A.L., Lombo C.G., Ahmed C., Thang M., Messenger E.J., Mumaw C.L., Johnson J.A., Kodavanti U.P., Oblak A.L., Et al., The bidirectional lung brain-axis of amyloid- β pathology: Ozone dysregulates the peri-plaque microenvironment, *Brain*, 146, pp. 991-1005, (2022); Park C., Hajat A., Leary C.S., Ilango S., Semmens E.O., Adam C., Fitzpatrick A.L., Lopez O.L., Kaufman J.D., Associations between long-term air pollution exposure and plasma amyloid beta in very old adults, *Alzheimer's Dement*, 17, (2021); Iaccarino L., La Joie R., Lesman-Segev O.H., Lee E., Hanna L., Allen I.E., Hillner B.E., Siegel B.A., Whitmer R.A., Carrillo M.C., Et al., Association Between Ambient Air Pollution and Amyloid Positron Emission Tomography Positivity in Older Adults With Cognitive Impairment, *JAMA Neurol*, 78, pp. 197-207, (2021); Duchesne

J., Gutierrez L.A., Chen J., Vienneau D., de Hoogh K., Jacquemin B., Ritchie K., Berr C., Mortamais M., Association between ambient air pollution exposure and plasma β -amyloid levels in the French Three-City study: Preliminary results, ISEE Conf. Abstr, 32, (2022)

Correspondence Address

J. Olloquequi; Department of Biochemistry and Physiology, Physiology Section, Faculty of Pharmacy and Food Science, Universitat de Barcelona, Barcelona, 08028, Spain; email: jordiolloquequi@ub.edu

Publisher

Multidisciplinary Digital Publishing Institute (MDPI)

ISSN

16616596

PubMed ID

39000036.0

Language of Original Document

English

Abbreviated Source Title

Int. J. Mol. Sci.

Document Type

Review

Publication Stage

Final

Source

Scopus

EID

2-s2.0-85198354075