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Influence of $PM_{2.5}$ on spermatogenesis dysfunction via the reactive-oxygen-species-mediated Mitogen-activated-protein-kinase signaling pathway

Abstract

Approximately 15 % of the world's couples confront childless, and about 50 % of them are due to male reproductive disorders. Several previous studies demonstrated that $PM_{2.5}$ particles has been consistently associated with critical human sperm reduction and impairment of human sperm chromatin and DNA from traffic exhaust pollution. Blood-testis barrier (BTB), a critically physical barrier between the seminiferous tubules and the blood vessels prevents sperm antigens from entering the blood circulation and facilitating and initiating an autoimmune response that contributing to spermatogenesis interference. Reactive oxygen species (ROS) are involved in the redox-sensitive signal transduction factors activation, such as Jun NH_2-terminal kinase (JNK), p 38, extracellular signal-regulated kinase (ERK), and mitogen-activated protein kinases (MAPK) that critically influence BTB disruption. After $PM_{2.5}$ exposure, there are decreased superoxide dismutase (SOD) expression, increased malondialdehyde (MDA) expression, increased nuclear factor erythroid 2-related factor 2 (*Nrf-2*) expression, increased expression of the four junctional proteins (β-catenin, Cx43, occludin, zonula occludens-1 (ZO-1)), thus improve sperm quality and quantity. $PM_{2.5}$ particles markedly induce increasing phosphorylation of MAPKs via the ROS-mediated MAPK signaling pathway that causes BTB disruption, but this effect is lesser in the vitamins C and E intervention as well as increasing cleaved caspase-3 expression and the Bcl-2/Bax ratio. In conclusion, combined therapeutic administration of vitamins C and E can maintain the BTB integrity, reduce oxidative stress and cell apoptosis, and prevent toxic effects.

Keywords: $PM_{2.5}$, spermatogenesis, ROS, MAPK

Volume 6 Issue 4 - 2019

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Received: August 16, 2019 | **Published:** August 30, 2019

Abbreviations: BTB, Blood-Testis Barrier; Cx43, Connexin 43; DNA, Deoxyribonucleic Acid; ESs, Ectoplasmic Specializations; ERK, Extracellular signal-Regulated Kinase; GJs, Gap Junctions; JNK, Jun NH_2-terminal Kinase; *Nrf-2*, Nuclear factor erythroid 2-Related Factor 2; MAPK, Mitogen-Activated Protein Kinase; MDA, Malondialdehyde; $PM_{2.5}$, Particulate Matter with diameter of 2.5 microns or less; ROS, Reactive Oxygen Species, SOD, Superoxide Dismutase; TJs, Tight Junctions; ZO-1, Zonula Occludens-1

Introduction

Globally, ambient fine particulate matter ($PM_{2.5}$) exposure has been an intractable health problem and associated with increased morbidity or mortality due to widespread excessive discharge of automobile exhaust and industrial development.[1–6] $PM_{2.5}$ can carry harmful and toxic substances deeply into the lungs and blood circulation, contributing damage to multiple organs, including reproductive system.[7] endocrine system,[8] nervous system.[9] Epidemiological data have demonstrated that approximately 15 % of the world's couples confront childlessness, and around 50% of these cases are due to male reproductive problems.[10,11] Previous studies revealed that $PM_{2.5}$ has consistently been related to significant sperm quality reduction,[12,13] as well as traffic exhaust pollution impairment of human sperm chromatin and deoxyribonucleic acid (DNA).[14]

Blood-Testis Barrier

The integrity of the blood-testis barrier (BTB) is critical for spermatogenesis in addition to the production of a large amount of sperm for maintenance of male reproductive function.[15,16] BTB, a physical barrier between the seminiferous tubules in the testes and the blood vessels, not only isolates harmful substances accessing to the seminiferous tubules, but also prevents sperm antigens from entering the blood stream and initiating an autoimmune response that interfering with spermatogenesis.[15,16] In mammals, BTB is one of the tightest blood-tissue barrier. BTB composes of desmosomes between Sertoli cells, tight junctions (TJs), gap junctions (GJs), and basal ectoplasmic specializations (ESs).[17] ESs, characteristic adhesion proteins main components of N-cadherin and β-catenin attached to testis, are the most typical and prominent ultrastructural features of the BTB.[18] GJs with an import GJ component " connexin 43 (Cx43) compose of gap junction proteins through docking with semi-channels between Sertoli cells and between Sertoli cells and germ cells,[19] whereas TJs with important components " occluding and zonula occludens-1 (ZO-1) " are formed by connective tissue structures between adjacent Sertoli cells with selective permeability.[20] Some previous studies demonstrated that after atmospheric $PM_{2.5}$ exposure, the BTB was severely damage, resulting in spermatogenesis dysfuntion and infertility.[21-23] Nevertheless, very few studies have investigated on the mechanism underlying these hazardous effects.[24-26]

Reactive oxygen species and mitogen-activated protein kinases

Reactive oxygen species (ROS) in the body are normally in a dynamic equilibrium association with antioxidants. $PM_{2.5}$ exposure induces excessive ROS production that is hazardous to male

reproductive system.[27] Several previous studies demonstrated that ROS are involved in the redox-sensitive signal transduction factors activation, such as Jun NH2-terminal kinase (JNK), p 38, extracellular signal-regulated kinase (ERK), and mitogen-activated protein kinases (MAPK).[21, 22, 28] BTB disruption is critically depended on these kinases.[29] MAPK pathway can activate *Nrf-2*, a transcription factor and the main regulator of antioxidant response elements that regulates antioxidant induction.[30] Spermatogenesis dysfunction has been caused by oxidative stress, whereas vitamins C and E have been demonstrated to reduce the impacts of environmentally toxic substances on the testes.[31-35] Nevertheless, very few studies have investigated the beneficial effects of vitamins C and E on $PM_{2.5}$-exposed spermatogenesis dysfunction, particularly from vehicle-exhaust-originated $PM_{2.5}$ exposures.

Discussion

Differences in the composition of $PM_{2.5}$ particles collected at different times and in different areas may contribute to diverse study results in human spermatogenesis although atmospheric $PM_{2.5}$ particles have been confirmed to significantly impair male spermatogenesis. Critically, the BTB is a barrier between the seminiferous tubules and the blood vessels. The BTB plays a significant role in protecting germ cells in the testes from toxic substances in the environment.[15] $PM_{2.5}$ from automobile exhaust facilitates spermatogenesis dysfunction via disruption of the BTB through the ROS-mediated MAPK signaling pathway. Combined vitamins C and E intervention effectively reduces $PM_{2.5}$-induced toxicity in the male reproductive system. Oxidative stress is related to significantly decreased effectiveness of antioxidant defenses or increased ROS production. Severe and persistent oxidative stress can trigger cell apoptosis.[36,37] After $PM_{2.5}$ exposure, superoxide dismutase (SOD) expression is significantly decreased, whereas malondialdehyde (MDA) and nuclear factor erythroid 2-related factor 2 (*Nrf-2*) expressions are significantly increased, indicating that excessive oxidative stress in the testes contributes to reduced SOD expression. Vitamins C and E can restore seminiferous tubule shape and cell layers of spermatogonia, spermatocytes, spermatids, Sertoli cells as well as increases the expression of the four junctional proteins (β-catenin, Cx43, occludin, zonula occludens-1 (ZO-1)), thus improve sperm quality and quantity. After $PM_{2.5}$ exposure, there is markedly increase of the phosphorylation of MAPKs via the ROS-mediated MAPK signaling pathway that causes BTB disruption, but this effect is lesser in the vitamins C and E intervention. Additionally, after $PM_{2.5}$ exposure, cleaved caspase-3 expression is increased and the Bcl-2/Bax ratio is decreased.

Conclusion

$PM_{2.5}$ particles disrupt BTB integrity by reduction of the expression of BTB-associated proteins, such as β-catenin, Cx43, occludin, and ZO-1. The BTB integrity is closely associated with the ROS-mediated MAPK signaling pathway. Combined therapeutic administration of vitamins C and E can maintain the BTB integrity, reduce oxidative stress and cell apoptosis, and prevent toxic effects.

Funding

The authors disclose no funding sources.

Acknowledgments

Dr. Attapon Cheepsattayakorn conducted the study framework and wrote the manuscript. Associate Professor Dr. Ruangrong Cheepsattayakorn contributed to scientific content and assistance in manuscript writing. Both authors read and approved the final version of the manuscript.

Conflicts of interest

The authors declare that they have no actual or potential competing financial interests.

References

1. Pope 3rd CA, Burnett RT, Turner MC, et al. Lung cancer and cardiovascular disease mortality associated with ambient air pollution and cigarette smoke: shape of the exposure-response relationships. *Environ Health Perspect.*. 2011;119(11):1616−1621.
2. Hou X, Strickland MJ, Liao KJ. Contributions of regional air pollutant emissions to ozone and fine particulate matter-related mortalities in eastern US urban area. *Environ Res.* 2015;137:475−484.
3. Cohen AJ, Brauer M, Burnett 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 Disease Study 2015. *Lancet.* 2017;389(10082):1907−1918.
4. Danysh HE, Mitchell LE, Zhang K, et al. Traffic-related air pollution and the incidence of childhood central nervous system tumors: Texas, 2001-2009. *Pediatr Blood Cancer.* 2015;62(9):1572−1578.
5. Franklin BA, Brook R, Arden Pope C. Air pollution and cardiovascular disease. *Curr Probl Cardiol.* 2015;40(5):207−238.
6. Holmes D. Endocrine disruptors: air pollution linked to insulin resistance. *Nat Rev Endocrinol.* 2016;12(12):688.
7. Watanabe N, Oonuki Y. Inhalation of diesel engine exhaust affects spermatogenesis in growing male rat. *Environ Health Perspect.* 1999;107(7):539−544.
8. Alink GM, Brouwer A, Heussen GA. Effects of outdoor and indoor airborne particulate matter on thyroid hormone and vitamin A metabolism. *Toxicol Lett.* 1994;72(1−3):73−81.
9. Wang Y, Xiong L, Tang M, et al. Toxicity of inhaled particulate matter on central nervous system: neuroinflammation, neuropsychological effects and neurodegenerative disease. *J Appl Toxicol.* 2017;37(6):644−667.
10. Inhorn MC, Patrizio P. Infertility around the globe: new thinking on gender, reproductive technologies and global movements in the 21th century. *Hum Reprod Update.* 2015;21(4):411−426.
11. Kilchevsky A, Honig S. Male factor infertility in 2011: semen quality, sperm selection, and hematospermia. *Nat Rev Urol.* 2012;9(2):68−70.
12. Hammoud A, Carrell DT, Gibson M, et al. Decreased sperm motility is associated with air pollution in Salt Lake City. *Fertil Steril.* 2010;93(6):1875−1879.
13. Zhou N, Cui Z, Yang S, et al. Air pollution and decreases semen quality : a comparative study of Chongqing urban and rural areas. *Environ Pollut.* 2014;187:145−152.
14. Calogero AE, La Vignera S, Condorelli RA, et al. Environmental car exhaust pollution damages human sperm chromatin and DNA. *J Endocrinol Invest.* 2011;34(6):e139−e143.
15. Cheng CY, Mruk DD. The blood-testis barrier and its implications for male contraception. *Pharmacol Rev.* 2012;64(1):16−64.
16. Wong CH, Cheng CY. The blood-testis barrier : its biology, regulation, and physiological role in spermatogenesis. *Curr Top Dev Biol.* 2005;71:263−296.
17. Mruk DD, Cheng CY. Sertoli-Sertoli and Sertoli-germ cell interactions and their significance in germ cell movement in the seminiferous epithelium during spermatogenesis. *Endocr Rev.* 2004;25(5):747−806.

18. Zhang J, Wong CH, Xia W, et al. Regulation of Sertoli-germ cell adherens junction dynamics via changes in protein-protein interactions of the N-cadherin-beta-catenin protein complex which are possibly mediated by c-Src and myotubularin-related protein 2: an *in vivo* study using an androgen suppression model. *Endocrinology.* 2005;146(3):1268−1284.
19. Pointis G, Segretain D. Role of connexin-based gap junction channels in testis. *Trends Endocrinol Metab.* 2005;16(7):300−306.
20. Mruk DD, Cheng CY. Tight junctions in the testis: new perspectives. *Philos Trans R Soc Lond B Biol Sci.* 2010;365(1546):1621−1635.
21. Cao J, Qin G, Shi R, et al. Overproduction of reactive oxygen species and activation of MAPKs are involved in apoptosis induced by $PM_{2.5}$ in rat cardiac H9c2 cells. *J Appl Toxicol.* 2016;36(4):609−617.
22. Cao XN, Yan C, Liu DY, et al. Fine particulate matter leads to reproductive impairment in male rats by overexpressing phosphatidylinositol 3-kinase (P13K)/protein kinase B (Akt) signaling pathway. *Toxicol Lett.* 2015;237(3):181−190.
23. Cao XN, Shen LJ, Wu SD, et al. Urban fine particulate matter exposure causes male reproductive injury through destroying blood-testis barrier (BTB) integrity. *Toxicol Lett.* 2017;266:1−12.
24. Che W, Qiu H, Liu G, et al. Oxidative damage of the extracts of condensate, particulate and semivolatile organic compounds from gasoline engine exhausts on testicles of rats. *Bull Environ Contam Toxicol.* 2009;83(1):42−47.
25. De Rosa M, Zarrilli S, Paesano L, et al. Traffic pollutants affect fertility in men. *Hum Reprod.* 2003;18(5):1055−1061.
26. Huang JY, Liao JW, Liu YC, et al. Motorcycle exhaust induces reproductive toxicity and testicular interleukin-6 in male rats. *Toxicol Sci.* 2008;103(1):137−148.
27. Bisht S, Dada R. Oxidative stress: major executioner in disease pathology, role in sperm DNA damage and preventive strategies. *Front Biosci.* 2017;9:420−447.
28. Oh PS, Lim KT. Blocking of intracellular ROS production by phytoglycoprotein (30 KDa) causes anti-proliferation in bisphenol A-stimulated Chang liver cells. *J Appl Toxicol.* 2008;28(6):749−758.
29. Almog T, Naor Z. The role of Mitogen-Activated Protein Kinase (MAPK) in sperm functions. *Mol Cell Endocrinol.* 2010;314(2):239−243.
30. Zhao M, Zhu P, Fujino M, et al. 5-Aminolevulinic acid with sodium ferrous citrate induces autophagy and protects cardiomyocytes from hypoxia-induced cellular injury through MAPK-Nrf-2-HO-1 signaling cascade. *Biochem Biophys Res Commun.* 2016;479(4):663−669.
31. Al-Damegh MA. Rat testicular impairment induced by electromagnetic radiation from a conventional cellular telephone and the protective effects of the antioxidants vitamins C and E. *Clinics.* 2012;67(7):785−792.
32. Ayinde OC, Ogunnowo S, Ogedegbe RA. Influence of vitamin C and vitamin E on testicular zinc content and testicular toxicity in lead exposed albino rats. *BMC Pharmacol Toxicol.* 2012;13:17.
33. Darican EK, Kalender Y. Dichlorvos-induced testicular toxicity in male rats and the protective role of vitamins C and E. *Exp Toxicol Pathol.* 2012;64(7−8):821−830.
34. Kanimozhi V, Palanivel K, Akbarsha MA, et al. Tributytin-mediated hepatic, renal and testicular tissue damage in male Syrian hamster (*Mesocricetus auratus*) : a study on impact of oxidative stress. *SpringerPlus.* 2016;5(1):1523.
35. Mukhopadhyay PK, Dey A, Mukherjee S, et al. The effect of coadministration of alpha-tocopherol and ascorbic acid on arsenic trioxide-induced testicular toxicity in adult rats. *J Basic Clin Physiol Pharmacol.* 2013;24(4):245−253.
36. Mazzoli-Rocha F, Fernandes S, Einicker-Lamas M, et al. Roles of oxidative stress in signaling and inflammation induced by particulate matter. *Cell Biol Toxicol.* 2010;26(5):481−498.
37. Møller P, Danielsen PH, Karottki DG, et al. Oxidative stress and inflammation generated DNA damage by exposure to air pollution particles. *Mutat Res Rev Mutat Res.* 2014;762:133−166.