ASIA PAC J PHARMACOTHER TOXICOL

OPEN ACCESS AMP Asian Medical Press

REVIEW ARTICLE

Received 17 Sep 2024 | Accepted 28 Sep 2024 | Published Online 05 Oct 2024 https://doi.org/10.32948/ajpt.2024.09.20

Effects of xenobiotics on the blood-brain barrier and neural gene expression

Mark Trussel[1], Jiff Brad[2]

Cite this article: Trussel M, Brad J: Effects of xenobiotics on the blood-brain barrier and neural gene expression. Asia Pac J Pharmacother Toxicol 2024, 4: 47-54. https://doi.org/10.32948/ajpt.2024.09.20

Abstract

The blood-brain barrier (BBB) is a selective barrier that restricts the entry of most substances from the bloodstream into the brain. It consists of three main components: endothelial cells, pericytes, and the astrocytic end-feet. The tight junctions (TJs) between endothelial cells contribute to the barrier's role in preventing many blood-derived substances from crossing into the brain. Xenobiotics refer to synthetic compounds commonly employed in domestic, agricultural, and industrial activities. They are found in the environment at both micropollutant and higher concentrations. These substances can be classified based on several factors, such as their origin, application, physical form, or effects on human health and the ecosystem. Their influence on both the environment and human health is significant. Compounds like argon (Ar), cadmium (Cd), chromium (Cr), and lead (Pb) have the ability to cross the BBB, causing alterations in the TJs and astrocytes, ultimately leading to BBB disruption. Disruption of the BBB, such as a compromised TJ seal, plays a significant role in the progression of various neurological conditions, including stroke and neuroinflammatory diseases. However, the potential of these compounds to penetrate and alter the BBB has not been widely explored. This review highlights the impact of xenobiotics on the central nervous system (CNS), particularly on the BBB. We will explore instances where their role in neurodegenerative processes is suspected. A particular attention is given to heavy metals, which pose a serious risk to human health, especially when they cross the BBB and accumulate in surrounding cells, triggering changes in the brain's environment that affect the entire body.

Key words blood-brain barrier, xenobiotics, heavy metals, toxic compounds

1. Feik School of Pharmacy, University of the Incarnate Word, 4301 Broadway, San Antonio, TX 78209, USA.

2. School of Health and Behavioral Sciences, University of the Sunshine Coast, 90 Sippy Downs Drive, Sippy Downs, Queensland 4556, Australia.

Correspondence: Mark Trussel (Feik School of Pharmacy, University of the Incarnate Word, 4301 Broadway, San Antonio, TX 78209, USA; E-mail: mark.trussel88@proton.me).

Introduction

The CNS is recognized as a highly complex structure. Neurons depend on a specific microenvironment that is fundamentally different from peripheral organs in terms of cellular and molecular characteristics. Vertebrate species have developed the blood-brain barrier (BBB) to maintain a clear division between the brain and the circulatory system [1]. The BBB is a highly specialized, semipermeable structure that tightly controls the exchange of substances between the CNS and the blood vessels. The BBB also blocks the entry of various therapeutic agents, nanocarriers, and their cargo [2, 3]. This indicates that the movement of substances from the bloodstream into the brain parenchyma is most effectively regulated at the blood-brain interface. Hence, the BBB is situated at the brain capillary endothelial cells, which tightly manage the exchange of metabolites [4].

Xenobiotics are chemical compounds that are foreign or unnatural to both human and animal systems. These substances encompass plant-derived components, pharmaceutical drugs, pesticides, cosmetic ingredients, artificial food flavors, fragrances, and more. Even naturally occurring compounds (endobiotics) can be classified as xenobiotics when present in elevated concentrations in environmental matrices [5]. Xenobiotics include pesticides, pharmaceutical compounds, personal care items, illicit drugs, industrial/commercial products, and nuclear waste, and can be found across various environmental media. These substances are utilized by humans and eventually make their way, directly or indirectly, into different environmental matrices, where they generate a range of metabolites and secondary products, some of which may be more toxic than the original compounds [6].

Xenobiotics can enter the body via inhalation, ingestion, and dermal absorption [7], making it difficult to control their exposure. When these substances infiltrate biological systems, they disrupt the homeostatic balance in the body, causing various effects, including gene alterations. These changes in genes can be either permanent or temporary. Xenobiotics influence gene expression by modulating epigenetic pathways, without any alterations to the DNA sequence [5, 8]. This in turn can lead to notable changes in brain function, with potential implications for neurological and neurodevelopmental disorders [9].

This review aims to examine the effects of various xenobiotics, such as heavy metals, on the BBB and brain function, focusing on the mechanisms by which these substances disrupt the BBB and the resulting functional and pathological changes in the brain.

Structure and function of the BBB

The challenge of the BBB in drug development for the brain was first recognized in 1914, coinciding with the rise of synthetic pharmaceuticals. In 1913, Ehrlich pioneered the creation of salvarsan and neosalvarsan, the earliest commercial antimicrobial drugs, which Hoechst introduced for syphilis treatment [10]. The BBB, integral to the NVU of the CNS, consists of various cell types arranged in several layers of biomaterials. The BBB includes the glycocalyx on its luminal surface, as well as two basement membranes: one associated with the vascular wall/endothelial cells and the other with the parenchymal region [11]. The composition of the BBB, including BMECs, pericytes, and astrocytes [12], is shown in **Figure 1**. BMECs exhibit reduced vesicular activity (fewer vesicles produced) and are interconnected by TJs [13]. These TJs significantly lower the permeability of the BBB, preventing harmful substances and pathogens from entering the brain parenchyma, thereby shielding it from inflammation, damage, and disease. Several molecules are actively included in the formation of TJs such as ZO-1, ZO-2, ZO-3, claudin-5, occludin, and JAMs [14, 15].These are anchored to cytoskeletal actin filaments and cingulin proteins, providing structural stability to the endothelial connections. As a result, only specific molecules can penetrate the brain parenchyma, mainly via receptor-mediated transcytosis through BMECs [11, 16, 17]. To better understand drug delivery strategies and the interaction between delivery systems and the brain, we will delve into the structure of the BBB.

Endothelial cells are the central anatomical component of the BBB, lining the cerebral blood vessels and interacting with various cell types within the CNS [18]. The endothelial cells of the BBB in the adult mammalian brain possess distinct characteristics that set them apart from ECs found in other parts of the body. They also differ from peripheral endothelial cells in function and morphology [19]. ECs are distinguished by their flattened shape, the presence of inter-endothelial tight junctions, a sparse number of caveolae on the luminal surface, and a higher concentration of mitochondria, especially when compared to endothelial cells from other vascular regions [12]. Endothelial cells are bound together by specialized TJs, which are significantly closer—50 to 100 times—than those found in peripheral capillaries. This proximity limits the passive movement of molecules into the brain and results in blood vessels having remarkably high transendothelial electrical resistance (TEER) [20]. These junctions are formed by claudin family proteins (Cldn) and occludin (Ocln), which are connected to the actin cytoskeleton through the ZO protein family (ZO-1, -2, -3) [21]. Any impairment in the regulation of these proteins compromises BBB integrity, allowing harmful substances into the brain and causing potential neurotoxicity or swelling [22]. Functionally, these cells possess a net negative surface charge, which hinders the binding of negatively charged molecules and leads to reduced expression of leukocyte adhesion molecules, limiting immune cell infiltration. Furthermore, they are equipped with specialized transporters that regulate the movement of specific substrates in and out of the cells. The number of transcellular vesicles traversing the vessel wall is minimized due to the high transendothelial electrical resistance [19].

Astrocytes, also referred to as astroglia, represent the largest population of glial cells and exhibit complex, polarized morphologies that vary across different brain regions [23]. Traditionally, they are classified into protoplasmic astrocytes, found in the well-vascularized gray matter, and fibrous astrocytes, located in the less vascularized white matter [24]. Astrocytes, known for their star-shaped structure, are highly prevalent and multifunctional cells that facilitate neuron migration during development and serve as buffers for potassium ions (K+) and neurotransmitters. These cells exhibit a stellate morphology with multiple extensions and are characterized by the expression of intermediate filament proteins such as vimentin (Vim) and glial fibrillary acidic protein (GFAP) [25]. Their end feet establish a connection with the basement membrane through the involvement of proteins such as aquaporin IV and the dystroglycan-dystrophin complex, which interact with the proteoglycan agrin [26-29]. In the CNS, they are vital for various functions, including waste clearance, blood flow regulation, vascular maintenance, ion balance, and neuroimmune response modulation [29, 30]. The junction between the astrocytic endfeet and the perivascular basal lamina is rich in organic anion transporters (OAPs), though their concentration decreases as the astrocytic membrane loses contact with the basal lamina [31]. This polarization of the astrocytic membrane is a notable structural feature of ACs in both mammals and birds, associated with the maturation of the BBB during development [12, 32].

Pericytes are cells that regulate blood-brain barrier development and function by controlling vascular permeability and inhibiting factors that increase immune cell infiltration into the CNS [33]. Pericytes play multiple roles in vascular function, such as controlling cerebral blood flow, supporting the integrity of the

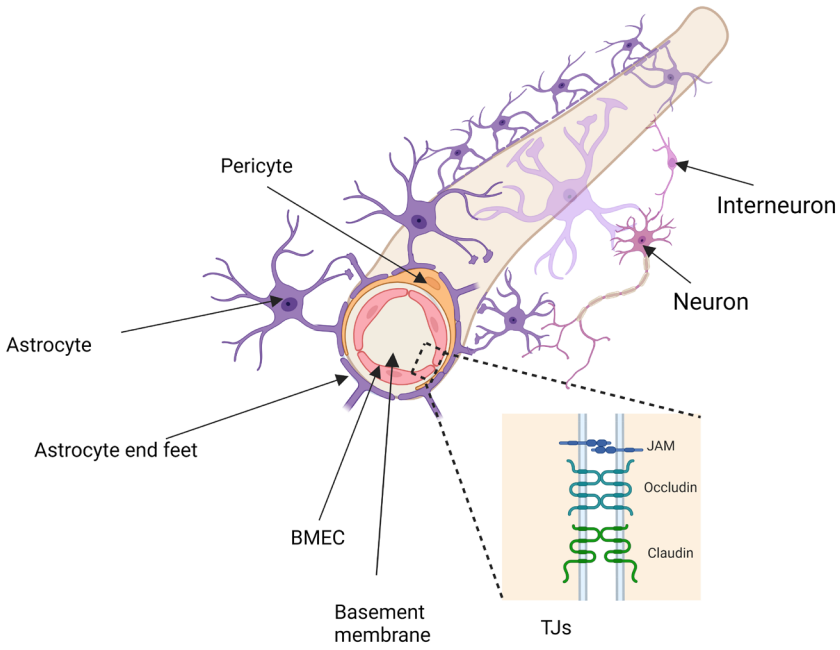

Figure 1. A schematic representation of the BBB, accompanied by a zoomed-in depiction of the tight junctions, (created by BioRender.com).

BBB, and guiding vascular development and angiogenesis. They are also capable of facilitating neuroinflammation and exhibit properties similar to stem cells [34]. Pericytes play a key role in the function of the neurovascular unit [35-37]. Their physical closeness to endothelial cells enables constant communication. One example of such interaction is the PDGF-B signaling pathway [38], where endothelial cells release PDGF-B to bind to PDGFRβ on pericytes, guiding their recruitment to the vasculature [39]. A decline in pericyte populations can disrupt tight junctions between ECs, thereby increasing the permeability of the BBB [40].

Tight junctions

Tight junctions serve as the primary functional elements in the BBB, ensuring the integrity of the permeability barrier and the maintenance of tissue homeostasis [41]. The endothelial cells in the BBB are held together by junction complexes, with TJs being particularly important in this arrangement [42]. TJs create a highly selective barrier that prevents most substances in the bloodstream from passing into the brain. They obstruct the paracellular aqueous diffusion pathways between neighboring endothelial cells. By adhering tightly, TJs seal microvessels, thereby hindering the passive movement of proteins and polar solutes into and out of the CNS [43].

Another important component of BBB is adhering junctions, these junctions form distinct microdomains at cellular interfaces, characterized by their spatial, chemical, and mechanical properties [44]. Like tight junctions, adherens junctions are linked to the cytoskeleton and contain both transmembrane and cytoplasmic plaque proteins [45]. Adherens junctions play an importan role role in preserving the BBB, and any disruption to these junctions may impair the connections between endothelial cells [46].

Xenobiotics and BBB disruption

Xenobiotics are substances that are foreign to biological systems, originating from the Greek term Xenos, meaning stranger. These include synthetic chemicals, such as drugs, pesticides, and carcinogens, that are not naturally found in living organisms or ecosystems [47]. Xenobiotics often used in household, agricultural, and industrial activities, are found in the environment in both trace amounts and higher concentrations (measured in ng/L to µg/L). These substances can be classified based on various factors such as their nature, usage, physical form, and pathophysiological effects. Their influence on human health and the environment is significant [48]. The physicochemical characteristics of xenobiotics, including their small molecular size, ionizability, water solubility, lipophilicity, polarity, and volatility, make it challenging to degrade, identify, and quantify these complex compounds [49]. Various environmental toxicants, including polycyclic aromatic hydrocarbons (PAHs), dioxins, heavy metals, perfluoroalkyl substances, and airborne pollutants, have been shown to disrupt the permeability of the BBB [50]. PAHs consist of aromatic rings, typically numbering between two and ten. Their lipophilic nature allows them to cross the BBB with ease, leading to brain damage, behavioral alterations, and neurodevelopmental problems [51]. For example, inhalation of diesel exhaust has been shown to disrupt BBB integrity, further supporting the argument that diesel exposure may elevate the risk of neurovascular conditions [52]. In both in vitro and in vivo studies, TCDD exposure stimulates the expression of xenobiotic-metabolizing enzymes, such as Cyp1a1 and Cyp1b1 [53]. These chemicals are known to be developmental neurotoxicants, affecting key processes in the developing brains of embryos and neonates [54]. A study found that administering three PCB congeners (75–150 µg/kg) to mice disrupted the function of blood-brain barrier tight junctions [55]. Wang et.al. reported that

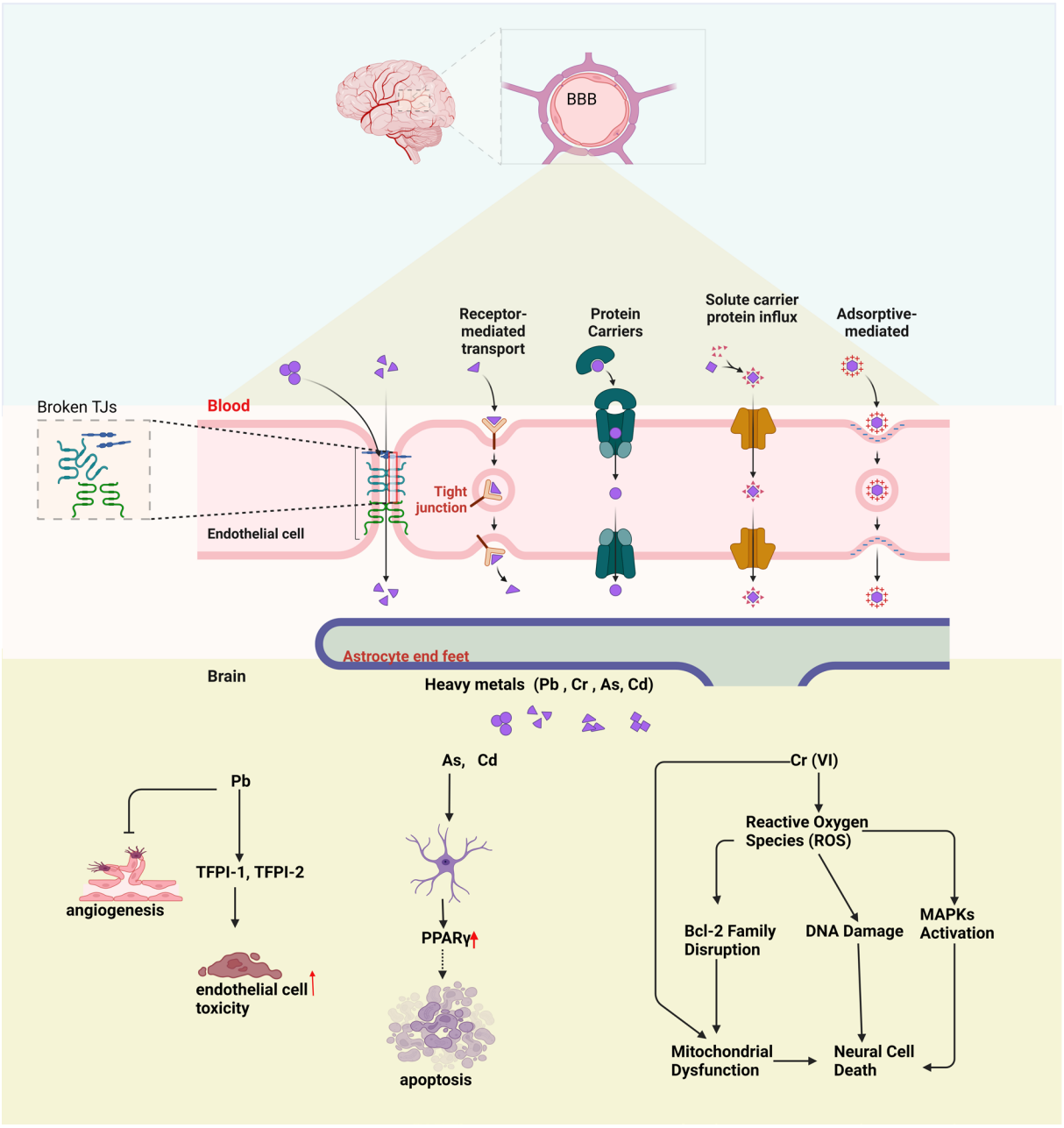

Figure 2. Schematic diagram of the BBB and the impact of heavy metal exposure on brain function. Disruption of TJs can lead to BBB damage. The lower section illustrates how heavy metals (Pb, Cr, As, Cd) affect brain cells: Pb causes endothelial toxicity, As and Cd trigger apoptosis via PPARγ, and Cr (VI) induces oxidative stress, leading to DNA damage, mitochondrial dysfunction, and neural cell death.

toxicants that interact with the aryl hydrocarbon receptor can affect xenobiotic efflux transporters at the BBB, leading to a reduction in the accumulation of central nervous system-active therapeutic drugs in the brain [56].

Gene expression changes in the brain induced by xenobiotics

The processes of transcription, translation, and subsequent protein modification involve the transfer of genetic information from the stable DNA archive to short-lived messenger RNA, typically leading to protein synthesis [57]. Even though all cells in an organism contain nearly identical DNA, their types and functions vary due to qualitative and quantitative differences in gene expression [58]. As a result, gene expression regulation is central to cellular differentiation and development [59]. The gene expression patterns specific to differentiated cells are established during development and are maintained as cells divide through mitosis [60]. In addition to inheriting genetic information, cells also inherit information beyond the DNA sequence itself, often referred to as epigenetic information. Epigenetics is described as the investigation of changes in gene expression that are mitotically (and possibly meiotically) inheritable, without involving alterations in the DNA sequence. However, some broader definitions of epigenetics do not strictly require heritability as a criterion [60]. The primary epigenetic mechanisms include DNA methylation, chromatin modifications, imprinting loss, and non-coding RNA. Epigenetic control of gene expression seems to have lasting and broad impacts on overall health [61]. Epigenetic mechanisms

regulate gene expression and are vital for proper brain activity. Therefore, any changes in these epigenetics may contribute to the development of brain disease [62].

Environmental factors including xenobiotics play a crucial role in epigenetic modulation, influencing cell differentiation both in early life and throughout the lifespan. These factors can actively regulate gene expression in a manner specific to different cells and tissues [63]. Genetic variations involve changes to the DNA sequence, whereas epigenetic regulation adjusts gene expression in response to environmental conditions, without altering the genome itself. Therefore, epigenetic mechanisms bridge the gap between environmental influences and genetic factors [64]. The epigenetic modification process involves chemical changes to chromatin and the regulation of miRNA expression [65]. Xenobiotics may exert broad systemic effects or target specific genomic regions, and they can influence the DNA methylome, histone modifications, or both. These compounds can either inhibit or enhance the activity of epigenetic modifiers. For instance, certain heavy metals impact DNMTs, histone deacetylases, and methyltransferases, ultimately regulating the epigenome. Additionally, xenobiotics may interfere with chemical moiety donors, such as arsenic disrupting SAM, the methyl group donor for DNA and histones, leading to epigenetic modifications [66, 67]. In some cases, these external substances can disrupt intermediary metabolism by altering levels of cofactors, co-enzymes, or substrate availability, or by affecting other enzymatic processes [68]. The epigenetic changes caused by xenobiotics may have either immediate or delayed effects, which could be transient or persist over the long term.

Effects of heavy metals on BBB integrity

Exposure to heavy metals has been associated with neuronal changes, with one of the key contributors to these changes being the disruption of the BBB [69]. A study reported that lead exposure may hasten Aβ1-42 accumulation in the brains of APP/PS1 mice, while also inducing abnormal alterations in the junction proteins of the BBB [70]. Another heavy metal, chromium, has been linked to the disruption of the BBB. Its accumulation in the hypothalamus can result in BBB impairment, neuronal structural abnormalities, synaptic degeneration, and gliosis, primarily through the activation of the Nrf2 and NF-κB signaling pathways [71]. Tetsuya T. and colleagues demonstrated that methylmercury causes damage to the BBB by upregulating *VEGF* expression in vivo [72]. Furthermore, a study found that compounds related to oil spills significantly impair the function of the BBB, which may explain the behavioral changes observed following crude oil exposure [73]. Exposure to aluminum has been linked to cognitive and behavioral deficits, damage to nerve cells, and the disruption of the blood-brain barrier. Aluminum exposure triggers pyroptosis by promoting NLRP3 inflammasome assembly, activating CASP1, and releasing pro-inflammatory cytokines IL-1β and IL-18, which contribute to the activation of microglia [74].

Tight junction proteins are particularly sensitive to environmental changes, and alterations in their microenvironment can lead to the dissociation of the occludin/ZO complex, which compromises the integrity of the BBB (**Figure 2**) [75]. A decrease in ZO-2 protein levels has been reported in cells exposed to Pb, further indicating altered BBB permeability in the model system studied [76]. Pb stimulation in C6 cells led to a decrease in ZO-1 (zonula occludens-1) and occludin protein levels in ECV304 cells [77]. Another investigation demonstrated that the TJ disruption is significantly influenced by the arsenic species and its chemical form [78]. The interaction of Cd with the vascular endothelium of the BBB led to the disruption of the TJ apparatus, which could subsequently cause secondary damage to the CNS [79]. Pb also upregulated the mRNA and protein expression of *MMP-2/9* in C6 cells. By inhibiting *MMP-2/9* with SB-3CT, we were able to partially reverse Pb-induced downregulation of tight junction proteins in ECV304 cells and reduce barrier impairment in the BBB model [77]. This suggests that the transport of these heavy metals may occur through various mechanisms, including the disruption of TJs.

Astrocytes are critical for maintaining homeostasis in the brain and executing a range of important tasks. They help regulate the blood-brain barrier, remove cellular debris, balance ions, control neurotransmitter levels, support neurogenesis and synaptogenesis, adjust synaptic connections, and release neurotrophins [80]. Astrocyte dysfunction can lead to the release of pro-inflammatory cytokines, destabilization of the blood-brain barrier, disruptions in glutamate and lipid metabolism, and eventually, the deterioration of synaptic integrity [81]. Astrocyte exposure to Cd, As and induced apoptosis by increasing the expression of peroxisome proliferator-activated receptor gamma (PPARγ) and promoting its interaction with the poly(ADP-ribose) polymerase (PARP) gene and PPARγ-response elements (PPREs) (**Figure 2**) [82].

A study reported that Pb is carried across an in vitro BBB model by a transporter with biochemical characteristics resembling those of the DMT1 isoform containing an iron-responsive element (IRE) [83]. Once it reaches BBB , Pb impairs endothelial cell function by reducing its viability (**Figure 2**). Exposure to Pb at concentrations of 3-100 μM exerted a cytotoxic effect on endothelial cells, inhibiting angiogenesis in a dose-dependent fashion. Pb disrupted normal EC physiological processes by interfering with the release of endogenous vascular protective mediators, TFPI-1 and TFPI-2. However, the negative impact of 3-30 μM Pb on the release of these mediators was successfully reversed by S-NACH in a concentration-dependent manner, restoring normal levels and mitigating Pb-induced angiogenesis disruption [84].

Conclusion

Current research focus on how xenobiotics cross brain barriers and their general effects on neurological diseases. However, understanding how these compounds interact with specific cells at a molecular level is important. Future studies should focus on the cell-specific mechanisms to understand how xenobiotics impact the BBB, potentially leading to targeted therapeutic interventions that could prevent or mitigate neurotoxic effects. For instance, astrocytes are essential for regulating the exchange of nutrients and maintaining the tight junctions that control BBB permeability. Changes in these cells could lead to neuroinflammation and cognitive decline. Pericytes also is a component of BBB that play a key role in maintaining the structural integrity of the BBB. Any damage to these cells could lead to BBB dysfunction, allowing harmful substances to infiltrate the brain and exacerbate neurological diseases.

Acknowledgments

No applicable.

Ethics approval

No applicable.

Data availability

The data will be available upon request.

Funding

None.

Authors' contribution

Mark Trussel and Jiff Brad contributed to draft, critical revision of the article. Mark Trussel approved the final version to be submited.

Competing interests

None.

References

1. Benz F, Liebner S: Structure and function of the blood–brain barrier (BBB). Handb Exp Pharmacol 2022, 273: 3-31.
2. Segarra M, Aburto MR, Acker-Palmer A: Blood–brain barrier dynamics to maintain brain homeostasis. Trends Neurosci 2021, 44(5): 393-405.
3. Zha S, Liu H, Li H, Li H, Wong K-L, All AH: Functionalized nanomaterials capable of crossing the blood–brain barrier. ACS nano 2024, 18(3): 1820-1845.
4. Pandit R, Chen L, Götz J: The blood-brain barrier: Physiology and strategies for drug delivery. Adv Drug Deliv Rev 2020, 165: 1-14.
5. Balasubramanian S, Gunasekaran K, Sasidharan S, Mathan VJ, Perumal E: MicroRNAs and xenobiotic toxicity: an overview. Toxicol Rep 2020, 7: 583-595.
6. Singh M, Mishra RC, Shah I, Wadhwa V, Mor V: Xenobiotics: Sources, Pathways, Degradation, and Risk Associated with Major Emphasis on Pharmaceutical Compounds. In: Xenobiotics in Urban Ecosystems: Sources, Distribution and Health Impacts. Epub ahead of print., edn.: Springer; 2023: 87-106.
7. Ortiz P, Torres-Sánchez A, López-Moreno A, Cerk K, Ruiz-Moreno Á, Monteoliva-Sánchez M, Ampatzoglou A, Aguilera M, Gruszecka-Kosowska A: Impact of cumulative environmental and dietary xenobiotics on human microbiota: risk assessment for one health. J Xenobiot 2022, 12(1): 56-63.
8. Burgos-Aceves MA, Cohen A, Paolella G, Lepretti M, Smith Y, Faggio C, Lionetti L: Modulation of mitochondrial functions by xenobiotic-induced microRNA: from environmental sentinel organisms to mammals. Sci Total Environ 2018, 645: 79-88.
9. Rock KD, Patisaul HB: Environmental mechanisms of neurodevelopmental toxicity. Curr Environ Health Rep 2018, 5(1): 145-157.
10. Ehrlich P: Address in pathology, ON CHEMIOTHERAPY: delivered before the Seventeenth International Congress of Medicine. Br Med J 1913, 2(2746): 353-359.
11. Shamul JG, Wang Z, Gong H, Ou W, White AM, Moniz-Garcia DP, Gu S, Clyne AM, Quiñones-Hinojosa A, He X: Meta-analysis of the make-up and properties of in vitro models of the healthy and diseased blood–brain barrier. Nat Biomed Eng 2024, Epub ahead of print.
12. Kadry H, Noorani B, Cucullo L: A blood–brain barrier overview on structure, function, impairment, and biomarkers of integrity. Fluids Barriers CNS 2020, 17(1): 69.
13. He Q, Liu J, Liang J, Liu X, Li W, Liu Z, Ding Z, Tuo D: Towards improvements for penetrating the blood–brain barrier—recent progress from a material and pharmaceutical perspective. Cells 2018, 7(4): 24.
14. Zhang W, Liu QY, Haqqani AS, Leclerc S, Liu Z, Fauteux F, Baumann E, Delaney CE, Ly D, Star AT, et al: Differential expression of receptors mediating receptor-mediated transcytosis (RMT) in brain microvessels, brain parenchyma and peripheral tissues of the mouse and the human. Fluids Barriers CNS 2020, 17(1): 47.
15. Greene C, Campbell M: Tight junction modulation of the blood brain barrier: CNS delivery of small molecules. Tissue Barriers 2016, 4(1): e1138017.
16. Bentivoglio M, Kristensson K: Tryps and trips: cell trafficking across the 100-year-old blood–brain barrier. Trends Neurosci 2014, 37(6): 325-333.
17. Bors LA, Erdő F: Overcoming the blood–brain barrier. challenges and tricks for CNS drug delivery. Scientia Pharmaceutica 2019, 87(1): 6.
18. Wolburg H, Noell S, Mack A, Wolburg-Buchholz K, Fallier-Becker P: Brain endothelial cells and the glio-vascular complex. Cell Tissue Res 2009, 335(1): 75-96.
19. Wu D, Chen Q, Chen X, Han F, Chen Z, Wang Y: The blood–brain barrier: structure, regulation, and drug delivery. Signal Transduct Target Ther 2023, 8(1): 217.
20. Nagasawa K, Chiba H, Fujita H, Kojima T, Saito T, Endo T, Sawada N: Possible involvement of gap junctions in the barrier function of tight junctions of brain and lung endothelial cells. J Cell Physiol 2006, 208(1): 123-132.
21. Roehlen N, Roca Suarez AA, El Saghire H, Saviano A, Schuster C, Lupberger J, Baumert TF: Tight junction proteins and the biology of hepatobiliary disease. Int J Mol Sci 2020, 21(3): 825.
22. Archie SR, Al Shoyaib A, Cucullo L: Blood-brain barrier dysfunction in CNS disorders and putative therapeutic targets: an overview. Pharmaceutics 2021, 13(11): 1779.
23. Yao S, Xu MD, Wang Y, Zhao ST, Wang J, Chen GF, Chen WB, Liu J, Huang GB, Sun WJ , et al: Astrocytic lactate dehydrogenase A regulates neuronal excitability and depressive-like behaviors through lactate homeostasis in mice. Nat Commun 2023, 14(1): 729.
24. Mayo F, González-Vinceiro L, Hiraldo-González L, Calle-Castillejo C, Morales-Alvarez S, Ramírez-Lorca R, Echevarría M: Aquaporin-4 expression switches from white to gray matter regions during postnatal development of the central nervous system. Int J Mol Sci 2023, 24(3): 3048.
25. Lien CF, Mohanta SK, Frontczak-Baniewicz M, Swinny JD, Zablocka B, Górecki DC: Absence of glial α-dystrobrevin causes abnormalities of the blood-brain barrier and progressive brain edema. J Biol Chem 2012, 287(49): 41374-41385.
26. Engelhardt B, Liebner S: Novel insights into the development and maintenance of the blood–brain barrier. Cell Tissue Res 2014, 355(3): 687-699.
27. Ezan P, André P, Cisternino S, Saubaméa B, Boulay A-C, Doutremer S, Thomas M-A, Quenech'Du N, Giaume C, Cohen-Salmon M: Deletion of astroglial connexins weakens the blood–brain barrier. J Cereb Blood Flow Metab 2012, 32(8): 1457-1467.
28. Nagelhus EA, Ottersen OP: Physiological roles of aquaporin-4 in brain. Physiol Rev 2013, 93(4): 1543-1562.
29. Kim DY, Zhang H, Park S, Kim Y, Bae C-R, Kim Y-M, Kwon Y-G: CU06-1004 (endothelial dysfunction blocker) ameliorates astrocyte end-feet swelling by stabilizing endothelial cell junctions in cerebral ischemia/reperfusion injury. J Mol Med (Berl) 2020, 98(6): 875-886.
30. Zhao J, Sun J, Zheng Y, Zheng Y, Shao Y, Li Y, Fei F, Xu C, Liu X, Wang S , et al: Activated astrocytes attenuate neocortical seizures in rodent models through driving Na(+)-K(+)-ATPase. Nat Commun 2022, 13(1): 7136.
31. Wolburg H, Wolburg-Buchholz K, Fallier-Becker P, Noell S, Mack AF: Structure and functions of aquaporin-4-based orthogonal arrays of particles. Int Rev Cell Mol Biol 2011, 287: 1-41.
32. Liebner S, Czupalla CJ, Wolburg H: Current concepts of blood-brain barrier development. Int J Dev Biol 2011, 55(4)-5: 467-476.
33. Daneman R, Zhou L, Kebede AA, Barres BA: Pericytes are required for blood–brain barrier integrity during embryogenesis. Nature 2010, 468(7323): 562-566.
34. Brown LS, Foster CG, Courtney J-M, King NE, Howells DW, Sutherland BA: Pericytes and neurovascular function in the healthy and diseased brain. Front Cell Neurosci 2019, 13: 282.
35. McConnell HL, Kersch CN, Woltjer RL, Neuwelt EA: The translational significance of the neurovascular unit. J Biol Chem 2017, 292(3): 762-770.
36. Liao K, Niu F, Hu G, Buch S: Morphine-mediated release of

astrocyte-derived extracellular vesicle miR-23a induces loss of pericyte coverage at the blood-brain barrier: Implications for neuroinflammation. Front Cell Dev Biol 2022, 10: 984375.
37. Goncalves A, Antonetti DA: Transgenic animal models to explore and modulate the blood brain and blood retinal barriers of the CNS. Fluids Barriers CNS 2022, 19(1): 86.
38. Jeske R, Albo J, Marzano M, Bejoy J, Li Y: Engineering brain-specific pericytes from human pluripotent stem cells. Tissue Engineering Part B: Reviews 2020, 26(4): 367-382.
39. Lee SJ, Kim S, Jo DH, Cho CS, Kim SR, Kang D, Chae J, Yoo DK, Ha S, Chung J , et al: Specific ablation of PDGFRβ-overexpressing pericytes with antibody-drug conjugate potently inhibits pathologic ocular neovascularization in mouse models. Commun Med (Lond) 2021, 1: 58.
40. Sengillo JD, Winkler EA, Walker CT, Sullivan JS, Johnson M, Zlokovic BV: Deficiency in Mural Vascular Cells Coincides with Blood–Brain Barrier Disruption in A lzheimer's Disease. Brain Pathol 2013, 23(3): 303-310.
41. Wolburg H, Lippoldt A: Tight junctions of the blood–brain barrier: development, composition and regulation. Vascul Pharmacol 2002, 38(6): 323-337.
42. Liu WY, Wang ZB, Zhang LC, Wei X, Li L: Tight junction in blood-brain barrier: an overview of structure, regulation, and regulator substances. CNS Neurosci Ther 2012, 18(8): 609-615.
43. Luissint A-C, Artus C, Glacial F, Ganeshamoorthy K, Couraud P-O: Tight junctions at the blood brain barrier: physiological architecture and disease-associated dysregulation. Fluids Barriers CNS 2012, 9(1): 1-12.
44. Kwak M, Southard KM, Kim WR, Lin A, Kim NH, Gopalappa R, Lee HJ, An M, Choi SH, Jung Y , et al: Adherens junctions organize size-selective proteolytic hotspots critical for Notch signalling. Nat Cell Biol 2022, 24(12): 1739-1753.
45. Malinova TS, Huveneers S: Sensing of cytoskeletal forces by asymmetric adherens junctions. Trends Cell Biol 2018, 28(4): 328-341.
46. Turowski P, Kenny B-A: The blood-brain barrier and methamphetamine: open sesame? Front Neurosci 2015, 9: 156.
47. Arya P, Haq SA: Effects of xenobiotics and their biodegradation in marine life. In: Smart bioremediation technologies. Epub ahead of print., edn.: Elsevier; 2019: 63-81.
48. Štefanac T, Grgas D, Landeka Dragičević T: Xenobiotics—division and methods of detection: a review. J Xenobiot 2021, 11(4): 130-141.
49. de Oliveira M, Frihling BEF, Velasques J, Magalhães Filho FJC, Cavalheri PS, Migliolo L: Pharmaceuticals residues and xenobiotics contaminants: occurrence, analytical techniques and sustainable alternatives for wastewater treatment. Sci Total Environ 2020, 705: 135568.
50. Kelly GC, Watase CK, Ho DH: Blood-brain barrier function as a biomarker in toxicology: Impact of environmental toxicants. In: Biomarkers in Toxicology. Epub ahead of print., edn.: Springer; 2023: 583-607.
51. Mortamais M, Pujol J, van Drooge BL, Macià D, Martínez-Vilavella G, Reynes C, Sabatier R, Rivas I, Grimalt J, Forns J , et al: Effect of exposure to polycyclic aromatic hydrocarbons on basal ganglia and attention-deficit hyperactivity disorder symptoms in primary school children. Environ Int 2017, 105: 12-19.
52. Heidari Nejad S, Takechi R, Mullins BJ, Giles C, Larcombe AN, Bertolatti D, Rumchev K, Dhaliwal S, Mamo J: The effect of diesel exhaust exposure on blood–brain barrier integrity and function in a murine model. J Appl Toxicol 2015, 35(1): 41-47.
53. Dauchy S, Miller F, Couraud P-O, Weaver RJ, Weksler B, Romero I-A, Scherrmann J-M, De Waziers I, Declèves X: Expression and transcriptional regulation of ABC transporters and cytochromes P450 in hCMEC/D3 human cerebral microvascular endothelial cells. Biochem Pharmacol 2009, 77(5): 897-909.
54. Collins LL, Williamson MA, Thompson BD, Dever DP, Gasiewicz TA, Opanashuk LA: 2, 3, 7, 8-Tetracholorodibenzo-p-dioxin exposure disrupts granule neuron precursor maturation in the developing mouse cerebellum. Toxicol Sci 2008, 103(1): 125-136.
55. Seelbach M, Chen L, Powell A, Choi YJ, Zhang B, Hennig B, Toborek M: Polychlorinated biphenyls disrupt blood–brain barrier integrity and promote brain metastasis formation. Environ Health Perspect 2010, 118(4): 479-484.
56. Wang X, Hawkins BT, Miller DS: Aryl hydrocarbon receptor-mediated up-regulation of ATP-driven xenobiotic efflux transporters at the blood-brain barrier. FASEB J2011, 25(2): 644-652.
57. Guo J: Transcription: the epicenter of gene expression. In., vol. 15: Springer; 2014: 409-411.
58. Alberts B, Johnson A, Lewis J, Raff M, Roberts K, Walter P: An overview of gene control. Molecular Biology of the Cell 4th edition 2002, Epub ahead of print.
59. Ralston A, Shaw K: Gene expression regulates cell differentiation. Nat Educ 2008, 1(1): 127-131.
60. Gibney E, Nolan C: Epigenetics and gene expression. Heredity 2010, 105(1): 4-13.
61. Hamilton JP: Epigenetics: principles and practice. Digestive diseases 2011, 29(2): 130-135.
62. Mallick R, Duttaroy AK: Epigenetic modification impacting brain functions: Effects of physical activity, micronutrients, caffeine, toxins, and addictive substances. Neurochem Int 2023, Epub ahead of print.: 105627.
63. Gabbianelli R: Modulation of the epigenome by nutrition and xenobiotics during early life and across the life span: the key role of lifestyle. Lifestyle Genom 2018, 11(1): 9-12.
64. Bird A: Perceptions of epigenetics. Nature 2007, 447(7143): 396-398.
65. Verma A, Maini J, Jain S, Ghasemi M, Kohli S, Brahmachari V: Epigenetic regulation and transcriptional memory in development; selection facilitating prudence. Int J Dev Biol 2020, 64(1-2-3): 181-201.
66. Yin R, Mo J, Dai J, Wang H: Nickel (II) inhibits tet-mediated 5-methylcytosine oxidation by high affinity displacement of the cofactor iron (II). ACS Chem Biol 2017, 12(6): 1494-1498.
67. Cheng TF, Choudhuri S, Muldoon-Jacobs K: Epigenetic targets of some toxicologically relevant metals: a review of the literature. J Appl Toxicol 2012, 32(9): 643-653.
68. Jiménez-Chillarón JC, Nijland MJ, Ascensão AA, Sardao VA, Magalhães J, Hitchler MJ, Domann FE, Oliveira PJ: Back to the future: transgenerational transmission of xenobiotic-induced epigenetic remodeling. Epigenetics 2015, 10(4): 259-273.
69. Bar-Or A, Nuttall RK, Duddy M, Alter A, Kim HJ, Ifergan I, Pennington CJ, Bourgoin P, Edwards DR, Yong VW: Analyses of all matrix metalloproteinase members in leukocytes emphasize monocytes as major inflammatory mediators in multiple sclerosis. Brain 2003, 126(12): 2738-2749.
70. Wu S, Liu H, Zhao H, Wang X, Chen J, Xia D, Xiao C, Cheng J, Zhao Z, He Y: Environmental lead exposure aggravates the progression of Alzheimer's disease in mice by targeting on blood brain barrier. Toxicol Lett 2020, 319: 138-147.
71. Ding J, Sun B, Gao Y, Zheng J, Liu C, Huang J, Jia N, Pei X, Jiang X, Hu S, et al: Evidence for chromium crosses blood brain barrier from the hypothalamus in chromium mice model. Ecotoxicol Environ Saf 2024, 273: 116179.
72. Takahashi T, Fujimura M, Koyama M, Kanazawa M, Usuki F, Nishizawa M, Shimohata T: Methylmercury causes blood-brain barrier damage in rats via upregulation of vascular endothelial growth factor expression. PLoS One 2017, 12(1): e0170623.
73. Ho DH, Burggren WW: Blood-brain barrier function, cell viability, and gene expression of tight junction-associated proteins in the mouse are disrupted by crude oil, benzo [a] pyrene, and the dispersant COREXIT. Comparati Biochemi and Physiol Part C: Toxicol & Pharmacol 2019, 223: 96-105.
74. Hao W, Hao C, Wu C, Xu Y, Wu S, Lu X, Yang J, Jin C: Aluminum

impairs cognitive function by activating DDX3X-NLRP3-mediated pyroptosis signaling pathway. Food Chem Toxicol 2021, 157: 112591.
75. Collins NT, Cummins PM, Colgan OC, Ferguson G, Birney YA, Murphy RP, Meade G, Cahill PA: Cyclic Strain–Mediated Regulation of Vascular Endothelial Occludin and ZO-1: Influence on Intercellular Tight Junction Assembly and Function. Arterioscler Thromb Vasc Biol 2006, 26(1): 62-68.
76. Tobwala S, Wang H-J, Carey JW, Banks WA, Ercal N: Effects of lead and cadmium on brain endothelial cell survival, monolayer permeability, and crucial oxidative stress markers in an in vitro model of the blood-brain barrier. Toxics 2014, 2(2): 258-275.
77. Liu X, Su P, Meng S, Aschner M, Cao Y, Luo W, Zheng G, Liu M: Role of matrix metalloproteinase-2/9 (MMP2/9) in lead-induced changes in an in vitro blood-brain barrier model. Int J Biol Sci 2017, 13(11): 1351-1360.
78. Yamauchi H, Hitomi T, Takata A: Evaluation of arsenic metabolism and tight junction injury after exposure to arsenite and monomethylarsonous acid using a rat in vitro blood–Brain barrier model. Plos one 2023, 18(11): e0295154.
79. Branca JJV, Maresca M, Morucci G, Mello T, Becatti M, Pazzagli L, Colzi I, Gonnelli C, Carrino D, Paternostro F, et al: Effects of Cadmium on ZO-1 Tight Junction Integrity of the Blood Brain Barrier. Int J Mol Sci 2019, 20(23): 6010.
80. Kwon HS, Koh S-H: Neuroinflammation in neurodegenerative disorders: the roles of microglia and astrocytes. Transl Neurodegener 2020, 9(1): 42.
81. Huang J, Li C, Shang H: Astrocytes in neurodegeneration: inspiration from genetics. Front Neurosci 2022, 16: 882316.
82. Kushwaha R, Mishra J, Tripathi S, Khare P, Bandyopadhyay S: Arsenic, cadmium, and lead like troglitazone trigger PPARγ-dependent poly (ADP-ribose) polymerase expression and subsequent apoptosis in rat brain astrocytes. Mol Neurobiol 2018, 55(3): 2125-2149.
83. Wang Q, Luo W, Zhang W, Liu M, Song H, Chen J: Involvement of DMT1+ IRE in the transport of lead in an in vitro BBB model. Toxicol in Vitro 2011, 25(4): 991-998.
84. Motawei SM, Sudha T, Yalcin M, Godugu K, Mousa SA: Lead-induced endothelial cell dysfunction: protective effect of sulfated non-anticoagulant low molecular weight heparin. Toxicol and Environ Health Sci 2021, 13: 123-131.