REVIEW

Effects of Natural Polyphenols on Blood–Brain Barrier Dysfunction Caused by Oxidative Stress

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ABSTRACT

The blood–brain barrier (BBB), which is made up primarily of brain microvascular endothelial cells and astrocytes linked by tight junctions (TJs) and adhesion molecules (AMs), keeps the brain parenchyma and extracellular fluid in a homeostatic balance. BBB disruption is a prevalent hallmark of neurodegenerative illnesses such as stroke, traumatic brain injury, and Alzheimer's disease, according to mounting data. Reactive oxygen species (ROS) are recognised to play a significant role in generating BBB disruption via TJ alteration, AM induction, cytoskeletal remodelling, and matrix metalloproteinase activation, among other pathological routes of BBB dysfunction. As a result, antioxidants may have a positive effect on BBB dysfunction-related brain illnesses. The origins of ROS production in different cells that make up or surround the BBB, such as BBB endothelial cells, astrocytes, microglia, and neutrophils, were covered in this review. We also looked at the numerous pathogenic pathways that ROS in these cells use to damage the BBB. Finally, we summarised the effects of several natural polyphenols on BBB dysfunction in order to propose a therapeutic strategy for brain illnesses caused by BBB disruption.

INTRODUCTION

The Blood–brain Barrier (BBB) is a structural membranous barrier that prevents chemicals from circulating in the blood from entering the brain and keeps the extracellular fluid in the brain in a homeostatic equilibrium under physiological settings. The BBB is made up primarily of brain microvascular Endothelial Cells (ECs), astrocytes, and pericytes, which have a few pinocytic vesicles, abundant mitochondria, interendothelial Tight Junctions (TJs), and adherens junctions and are characterised by a few pinocytic vesicles, abundant mitochondria, interendothelial Tight Junctions (TJs), and Adherens Junctions (AJs) [1]. While the BBB's low pinocytic activity inhibits transcellular transport of molecules across it, TJ proteins like claudin and occludin, as well as AJ proteins like cadherin and catenin, can regulate its paracellular permeability. Occludin and claudins are known to be anchored to BBB endothelial cells by scaffolding proteins such as ZO-1, ZO-2, and ZO-3, which belong to the Zonula Occludens (ZO) protein family. The permeability of the BBB is intimately related with the expression of TJ proteins and AJ proteins, such as claudin and cadherin, respectively. Indeed, increased occludin expression has been demonstrated to reduce permeability across the BBB by generating a decrease in paracellular transport, while increased claudin-5 expression reduces big molecule transit [2].

Disruption of the BBB is widespread in pathological situations and plays a key role in the pathogenesis of several cerebrovascular illnesses, such as stroke and Alzheimer's Disease (AD). By stimulating signalling pathways that mediate the breakdown of TJ proteins and the alteration of AJ proteins, Reactive Oxygen Species (ROS) play a crucial role in the disruption of the BBB. The involvement of ROS in the activation of Matrix Metalloproteinases (MMPs), a family of proteolytic enzymes that can destroy extracellular matrix components and disrupt the BBB, is also becoming clearer. Carotenoids (xanthophylls and carotenes), vitamins (vitamin E and C), and polyphenols are the most common antioxidants (phenolic acids, flavonoids, anthocyanins, lignans, and stilbenes) [3]. Compared to carotenoids, which are the principal scavengers of ROS such singlet oxygen and peroxy radicals, and vitamin C, which is a chain-disrupting scavenger of peroxy radicals, vitamin C is a chain-disrupting scavenger of peroxy radicals. Polyphenols are the most abundant and extensively distributed bioactive compounds, and they play a major role in the total antioxidant capabilities of many foods. Polyphenols are beneficial because they have a variety of antioxidant properties, including ROS suppression, inactivation of ROS precursors, metal chelation, and ROS scavenging. Polyphenols have

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also been found to be effective in the treatment of disorders such as cancer, type 2 diabetes, cardiovascular disease, and cerebrovascular disease. Polyphenols are beneficial because they have a variety of antioxidant properties, including ROS suppression, inactivation of ROS precursors, metal chelation, and ROS scavenging. Polyphenols have also been found to be effective in the treatment of disorders such as cancer, type 2 diabetes, cardiovascular disease, and cerebrovascular disease [4].

Multiple Cells That Make Up or Surround the BBB Experience Oxidative Stress

Low levels of ROS generation within vascular cells are well controlled by the endogenous antioxidant system, which includes key signalling molecules for optimal vascular function, under normal physiologic settings. The physiological impact of ROS is increasingly being demonstrated to be dependent on their intracellular quantities, chemical composition, and subcellular localisation. As a result, improper ROS scavenging may create paradoxical reductive stress and, as a result, pathological illness. Furthermore, oxidative stress is caused by an imbalance in the production of reactive oxygen species (ROS) and has a role in the development of a variety of diseases, including atherosclerosis, inflammatory diseases, and neurodegenerative disorders [5,6]. Excess ROS in the BBB can activate a number of signalling molecules, including hypoxia-inducible factor-1, nuclear factor kappa-lightchain-enhancer of activated B cells (NF-B), and MMPs, resulting in BBB malfunction and loss of integrity. BBB ECs and astrocytes, as well as the cells surrounding the BBB, are rich in mitochondria, which are one of the principal generators of ROS, especially under pathological conditions. Although mitochondrial ROS have lately been linked to cerebrovascular illness, little is known about their role in individual cells throughout the BBB disruption process. Other ROS generators, such as Nitric Oxide Synthase (NOS) and Nicotinamide Adenine Dinucleotide Phosphate (NADPH) oxidase, have been the subject of several investigations (NOX). Another source of ROS generation could be NOS [7]. The NOS family consists of three members: neuronal NOS (nNOS), endothelial NOS (eNOS), both of which are Ca2+-dependent enzymes that are constitutively expressed, and inducible NOS (iNOS), which can be expressed Ca2+-independently [38]. Under pathophysiological conditions, abnormal eNOS expression can contribute to the development of vascular disease by increasing oxidative stress (ONOO-) and converting eNOS to an O2-producing enzyme (uncoupled eNOS), which generates O2- rather than NO due to the tetrahydrobiopterin's decreased bioavailability (BH4, cofactor). As a result, abnormal eNOS production in BBB ECs is likely to be the cause of increased ONOO- protein tyrosine nitration, resulting in BBB rupture [8].

In BBB ECs, COXs and XOs are also potential ROS generators. COXs are heme-containing enzymes that catalyse the conversion of Arachidonic Acid (AA) to Prostaglandins (PGs), which are also a major source of Reactive Oxygen Species (ROS) in the brain and BBB ECs. COX has two primary isoforms: COX-1 is a housekeeping enzyme that is expressed in all tissues, while COX-2 can cause inflammation and is found in the renal medulla and renal pelvis, the gastrointestinal tract, the lung, the thymus, and the brain. Angiotensin II (AII) boosted ROS formation in bEnd3 cells via upregulating COX-2 expression, according to a recent study. After oxygen deprivation, XO also produces ROS in BBB ECs [9].

Oxidative Stress in Astrocytes during BBB Injury

Astrocytes are essential for the central nervous system's physiological tasks, including as nourishing neurons, maintaining BBB integrity, controlling synaptic activity, and processing cellular metabolites. Physiologically, astrocytes can protect the CNS from oxidative stress-induced damage by acting as antioxidants, but in pathological situations, they are one of the main generators of harmful ROS and Reactive Nitrogen Species (RNS). The condition of astrocytes changes from resting to reactive during brain injury, and reactive astrocytes have both protective and harmful activities. Astrocytes also express iNOS, and the RNS they produce are a crucial component of oxidative stress imposed by astrocytes. Lipopolysaccharide (LPS) was found to stimulate iNOS expression, resulting in NO generation, in an in vitro astrocyte culture research. The activation of iNOS in astrocytes by NFB is linked to brain damage caused by severe systemic inflammation. Furthermore, NO produced by iNOS resulted in aggregation of Superoxide Dismutase 1 (SOD1) via S-nitrosylation of protein disulfide isomerase in an in vitro I/R model of astrocytes, which may be relevant to the pathophysiology of the injury.

Oxidative Stress in Microglia during BBB Injury

Microglia, or brain-resident macrophages, have long been recognised as dynamic mediators of cerebrovascular illness. These phagocytic glial cells constitute a complex network that can respond to damage and pathogen-associated cues, mediating either protective or detrimental brain injury responses. Damage-associated Molecular Patterns (DAMPs), chemicals generated by injured neurons, elicit a response from microglia. This causes disease-associated microglia to become activated (DAM). Microglial activation and oxidative stress have a significant relationship, which leads to neurovascular damage [10,11].

Oxidative Stress in Neutrophil during BBB Injury

Neutrophils are phagocytic immune cells found in the bloodstream that are associated with acute inflammation. Chemotaxis is the process by which neutrophils transmigrate to the site of damage in response to chemical cues such as IL-8, complement component 5a, N-formyl methionyl-leucyl-phenylalanine, and H2O2 during the acute phase of inflammation [12]. Neutrophils perform a variety of roles in the ischemic brain, including ROS generation, phagocytosis, degranulation, and the release of neutrophil extracellular traps (NETs), all of which contribute to increased BBB permeability.

Role of Oxidative Stress in BBB Dysfunction

Modification of TJ proteins, elevation of Adhesion Molecules (AMs) expression, cytoskeletal reorganisation, MMP activation, and NET formation and release of pro-inflammatory mediators are all involved in triggering BBB failure. Cell adhesion is a process in which cells

attach to one other or to the Extracellular Matrix (ECM). AMs are a group of cell surface proteins that are involved in this process. Cleavage of VE-cadherin, phosphorylation, redistribution, and decreased expression of TJ proteins can all reduce junction integrity. BBB disruption can also be triggered by cytoskeleton rearrangement due to stress fibre production, phosphorylation of TJ proteins, FAK, and Faxillin, and phosphorylation of TJ proteins, FAK, and Faxillin. Adherent neutrophils, active astrocytes, and activated microglia and activated astrocytes can all generate pro-inflammatory mediators, as well as VEGF. NETs, activated astrocytes, VEGF, and ECs can all release MMPs [13].

TJ Proteins

TJ proteins, which operate as gatekeepers of the paracellular space between BBB ECs, govern the movement of water-soluble compounds and ions across the BBB, are largely responsible for the BBB's barrier function. Claudins, occludins, and ZO proteins are the three proteins that make up TJs. The primary isoforms of claudins (20–24 kDa) found in brain ECs are claudin-1, -3, -5, and -12, with claudin-5 being particularly well known for preventing paracellular diffusion of big particles via the BBB. Occludin is the TJs' principal structural protein, and its level of expression can reflect the BBB's structural integrity; for example, lower levels of occludin can indicate more BBB permeability [14]. ZOs (ZO-1, ZO-2, and ZO-3) are cytoskeleton scaffolding proteins that interact with intracellular components like F-actin to impact cytoskeleton mobility and other functions.

AMs

While AMs are inhibited in the absence of stimulation, they are momentarily coordinated to allow leukocyte rolling and firm adhesion/emigration to occur for several hours after the onset of an inflammatory response. The expression of AMs, which alter BBB permeability via mediating leukocyte-vascular adhesion and infiltration to the brain, has been demonstrated to be induced by oxidative stress. As a result, inhibiting the production of AMs may help to avoid BBB dysfunction. Oxidative stress also activates NF-B, which leads to the production of ICAM-1 and VCAM-1, and the crosslinking of ICAM-1 activates the Ca2+ signalling pathways, causing cytoskeletal changes and breaking the BBB. In Wistar rats, inhibiting ICAM-1 with an antibody prevents ischemic brain injury [15-17]. Similarly, removing ICAM-1 or neutrophils from a rat stroke model reduced infarct volume, decreased mortality, and improved BBB functioning.

Effects of Natural Polyphenols on BBB Dysfunction

Plants create natural polyphenols as secondary metabolites to defend themselves from other species. Polyphenols are divided into flavonoids (flavonols, flavones, flavanols, flavanones, isoflavones, and anthocyanins) and non-flavonoids (flavonols, flavones, flavanones, isoflavones, and anthocyanins) based on their "typical polyphenol structure" (i.e., multiple hydroxyl groups on aromatic rings) (stilbenes, phenolic acids lignans, tannins, and hydroxycinnamic acids). Polyphenols are powerful antioxidants that can either neutralise ROS by donating an electron or hydrogen atom, or decrease ROS development by blocking ROS synthesis.

Flavonoids

Flavonoids are phenolic chemicals that can be found in a variety of foods, including fruits, seeds, nuts, cereals, spices, wine, and tea. By scavenging ROS and UV absorption, they contribute to flower colour and minimise plant stress responses [18]. They can also have pharmacological properties like antioxidant, anti-inflammatory, and anticancer properties. Subgroups of flavonoids include flavonols, flavones, flavanols, flavanones, isoflavones, and chalcones.

Flavonols-Quercetin/Kaempferol/Rutin

Quercetin protects the BBB by controlling the generation of Reactive Oxygen Species (ROS). In human BBB EC, quercetin not only prevented BBB disruption but also mitigated enhanced BBB permeability by avoiding ROS overproduction and maintained SOD activity in fibrillar A-induced BBB damage. In a rat model of cerebral I/R damage, quercetin reduced brain edoema and improved BBB functioning by decreasing BBB permeability, upregulating the expression of tight junctions such claudin-5 and ZO-1, and inhibiting MMP-9 production, which is linked to the Wnt/-catenin signalling pathway [19].

CONCLUSION

Under healthy conditions, the BBB serves a crucial function in maintaining the homeostatic balance between the brain parenchyma and systemic circulation, but it can be disrupted under pathological situations. BBB breakdown appears to be a critical mechanism in a variety of neuroinflammatory illnesses, including stroke and Alzheimer's disease, according to mounting data. Targeting oxidative stress and BBB disruption may be a promising treatment method for neuroinflammatory disorders, as BBB malfunction has been linked to oxidative stress. We focused on the mechanisms involved in the formation of oxidative stress in cells that make up or surround the BBB under pathological situations in this review. We also discovered that ROS can activate TJ, AJ, cytoskeletal rearrangement, and MMP activation in cells involved with the BBB via a variety of signalling mechanisms.

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