Myeloperoxidase: a new target for the treatment of stroke?

From the Contents

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Abstract

Myeloperoxidase is an important inflammatory factor in the myeloid system, primarily expressed in neutrophils and microglia. Myeloperoxidase and its active products participate in the occurrence and development of hemorrhagic and ischemic stroke, including damage to the blood-brain barrier and brain. As a specific inflammatory marker, myeloperoxidase can be used in the evaluation of vascular disease occurrence and development in stroke, and a large amount of experimental and clinical data has indicated that the inhibition or lack of myeloperoxidase has positive impacts on stroke prognosis. Many studies have also shown that there is a correlation between the overexpression of myeloperoxidase and the risk of stroke. The occurrence of stroke not only refers to the first occurrence but also includes recurrence. Therefore, myeloperoxidase is significant for the clinical evaluation and prognosis of stroke. This paper reviews the potential role played by myeloperoxidase in the development of vascular injury and secondary brain injury after stroke and explores the effects of inhibiting myeloperoxidase on stroke prognosis. This paper also analyzes the significance of myeloperoxidase etiology in the occurrence and development of stroke and discusses whether myeloperoxidase can be used as a target for the treatment and prediction of stroke.

Key Words: blood-brain barrier; hemorrhagic stroke; inflammation; ischemic stroke; microglia; myeloperoxidase; neutrophils; secondary brain injury; stroke

Introduction

Stroke refers to a series of cerebrovascular diseases that cause brain damage due to changes in blood flow and oxygen delivery mediated by blood vessels. Depending on whether the cause of stroke is central nervous system hemorrhage or thrombotic ischemia, stroke can be classified as ischemic stroke and hemorrhagic stroke (Bedard and Krause, 2007; Liang et al., 2020), and ischemic stroke is the most common type, accounting for approximately 70% of all strokes. According to the 2017 Global Burden of Disease study (GBD), stroke is responsible for more than 5% of all disability-adjusted life years, and stroke was responsible for 11% of all deaths worldwide, which is equivalent to 6.17 million deaths due to stroke each year, ranking third among all causes of death (GBD 2016 DALYs and HALE Collaborators, 2017; GBD 2017 Causes of Death Collaborators, 2018; Avan et al., 2019; Deuschl et al., 2020). The GBD 2016 Lifetime Risk of Stroke Collaborators (2018), involving GBDs in various regions of the world, was published by the *New England Journal of Medicine*. The results showed over the past 26 years, the global risk of lifelong stroke among adults increased by 8.9% to 24.9% (95% confidence interval [CI] 23.5–26.2%), with a male risk of 24.7% (95% CI 23.3–26.0%) and a female risk of 25.1% (95% CI 23.7–26.5%), indicating that almost one-quarter of all adults are at risk of experience stroke during their lifetimes. Among all adults included in relevant studies, 18.3% are likely to experience an ischemic stroke, and 8.2% are likely to experience a hemorrhagic stroke. During the period from 1990 to 2016, the stroke incidence in China increased from 204.52 to 403.08 per 100,000 population, and mortality increased from 122.09 to 130.94 per 100,000 population (Wang et al., 2020). High blood pressure, heart disease, diabetes, atherosclerosis, lack of exercise, high blood fat, high-salt diet, smoking, alcoholism, and age have been identified as risk factors for stroke (George, 2020; Mai and Liang, 2020; Zhang et al., 2020). After stroke, the inflammatory system is activated. During the early stages of hemorrhagic stroke, the brain tissue surrounding the hematoma is characterized by the infiltration of inflammatory cells and inflammatory factors, such as free radicals and proteases, produced by neurons. These early inflammatory factors, including myeloperoxidase (MPO), continue to damage the brain during the whole process of the hematoma incident (Wang, 2010).

MPO is an important inflammatory factor in the myeloid system (Klebanoff, 2005). Agner (1941) first isolated and purified the heme peroxidase-containing MPO from the green purulent fluid obtained from tuberculosis patients; due to its green appearance, MPO is also known as verdoperoxidase (Klebanoff, 2005; Ray and Katyal, 2016). MPO is abundantly expressed in neutrophils and other myeloid cells, such as Ly-6Chigh monocytes (Swirski et al., 2009; Grishkovskaya et al., 2017), macrophages, and microglia (Gray et al., 2008; Gellhaar et al., 2017). After acute cerebral ischemia, due to the destruction of the blood–brain barrier (BBB), the infiltration of a large number of neutrophils attacks the central nervous system. Studies have shown

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that the large growth in the neutrophil population is accompanied by a large increase in MPO production (Gorudko et al., 2017; Reber et al., 2017; Pleskova et al., 2018; Maestrini et al., 2020). Large amounts of inflammation are observed during the early stages of stroke, and the activation of phagosomes represents an important form of inflammation. MPO is an important enzyme in phagocytic vacuoles. Among the antimicrobial systems present in the phagosome, a significant proportion consists of MPO, hydrogen peroxide (H_2O_2, formed during the respiratory burst), and a halide (X^-), particularly chloride (Cl^-) (Iana and Sirbu, 2020; Marcinkiewicz and Walczewska, 2020). In the MPO-H_2O_2-Cl^- sterilization system, the oxidant chlorous acid/hypochlorite ion ($HOCl/OCl^-$) plays an important role; under pathological conditions, a sustained inflammatory effect is exerted due to the activation of this system. Here, we outline the etiology of MPO production and its contributions during the occurrence and development of stroke, evaluate its feasibility for use as an indicator in clinical applications, and discuss whether it can serve as a target for stroke treatment and prognostic prediction.

Search Strategy

In the MEDLINE database, we searched for related articles using the English search terms "stroke, myeloperoxidase" in the limited time range from January 1990 to December 2020, and a total of 315 related articles were retrieved. The inclusion criteria were articles directly related to myeloperoxidase-associated stroke research and corresponding previous basic research; and similar research ideas selected from the latest articles published in authoritative journals. Exclusion criteria were repetitive or retrospective studies. Two researchers (YCW and YBL) independently read and screened the articles by reading the titles and abstracts and then combined the screening results. After the readers reported controversial documents, YNZ and YWP discussed whether to include them. Any articles unrelated to stroke and myeloperoxidase and among highly similar studies, only the most recently published article was retained. In the end, 106 articles were included in the reference catalog.

The Etiology of Myeloperoxidase in Stroke

The role of MPO in vascular injury before stroke
Stroke is classified as a vascular disease. When blood vessels are damaged due to malformations in arteriovenous blood vessels, a thrombus can form, leading to ischemic stroke, whereas hemorrhagic stroke results from the rupture of cerebral vessels. As a cornerstone of the pathophysiological mechanisms of these vascular diseases, MPO damages the arterial wall through either direct oxidation reactions with components of the arterial wall or indirect damage exerted on the integrity and function of the blood vessel (**Figure 1**). Indirect damage includes (i) the promotion of atherosclerotic plaque formation of foamy macrophages, resulting in the formation of a core rich in low-density lipoproteins; (ii) changes in serum cholesterol function, distribution, and flow due to lipid peroxidation; (iii) promoting the rupture and instability of atherosclerotic plaques due to matrix metalloproteinase (MMP) activation; (iv) the stimulation of local occlusive thrombosis through P-selectin interactions; and (v) the impairment of vascular reactivity through the depletion of endothelial-derived nitric oxide (NO), damaging vasodilatation and anti-inflammatory properties (Vita et al., 2004; Lau and Baldus, 2006; Nicholls and Hazen, 2009).

Molecular damage mechanisms mediated by MPO after stroke
The BBB is a highly specialized system for restricting interactions between the brain parenchyma and the bloodstream, promoting the maintenance of brain homeostasis. After a stroke, damage to the BBB is an important contributor to cerebral edema and hemorrhagic transformation (Lin et al., 2018). BBB damage can promote lacunar infarction, white matter lesions, and microhemorrhages in deep brain structures and trigger the production of a large number of neurotoxic substances, which damage synapses and neuronal function (Lin et al., 2018). The BBB becomes compromised after a stroke, allowing many immune cells to enter the central nervous system, where they interact with central immune cells to further aggravate the inflammatory response. Üllen et al. (2013) demonstrated that MPO produced by neutrophils induces the dysfunction of primary brain microvascular endothelial cells (BMVEC) *in vitro*, exacerbating the damage to the BBB. Klinke et al. (2011) revealed a previously unknown neutrophil recruitment mechanism induced by the electrostatic activity of MPO. These findings indicate that MPO and neutrophils have an interaction relationship in addition to a simple cascade reaction. El Kebir et al. (2008) further revealed that MPO

could delay neutrophil apoptosis by signaling the adhesion molecule CD11b/CD18, prolonging the inflammatory response. Therefore, MPO serves to enhance the duration of the inflammatory response, which can cause the brain tissue to undergo continual inflammatory damaged long after the stroke has resolved (Babior, 1984). Kang et al. (2020) showed that neutrophils accumulate in the peri-infarct cortex during all stages of ischemic stroke. Neutrophils produce intravascular and intraparenchymal extracellular neutrophil traps, which peak at 3–5 days. Extracellular neutrophil traps release many cytotoxic proteases, such as histones, elastase, and MPO, which directly induce endothelial cell damage to increase vascular permeability (Villanueva et al., 2011). The infiltration of neutrophils can upregulate peptidyl arginine deiminase 4, stimulator of interferon genes, and interferon regulatory factor 3. Peptidyl arginine deiminase 4 is a key enzyme involved in chromatin decondensation (Wang et al., 2009; Martinod et al., 2013). Stimulator of interferon genes is a DNA sensor, and the upregulation of interferon regulatory factor 3 can induce the production of interferon-β in large quantities, which can disrupt vascular reconstruction and vascular repair after stroke (Kang et al., 2020).

Microglia are another innate immune cell type in the nervous system associated with MPO, which plays a crucial role after stroke occurrence (Qin et al., 2019; Xu et al., 2021). After a stroke occurs, the function of microglia primarily depends on the activation signal received (Ma et al., 2017; Al Mamun et al., 2018). M1 type microglia represent a pro-inflammatory cell type, which primarily contributes to the early stages of stroke and can produce tumor necrosis factor-α (Feng et al., 2017), interleukin (IL)-1β (Facci et al., 2018), interferon-γ (Hwang and Bergmann, 2020), inducible NO synthase (Maksoud et al., 2021), and proteolytic enzymes (MMP9 and MMP3) (Bonetti et al., 2019). During the later stage of stroke, M2 type microglia exert anti-inflammatory effects (Jiang et al., 2018), producing IL-10 (Lobo-Silva et al., 2017), transforming growth factor β (Spittau et al., 2020), insulin-like growth factor (Li et al., 2020), and vascular endothelial growth factor (Ju et al., 2019), which are pro-angiogenic and anti-inflammatory (Ponomarev et al., 2013). Therefore, MPO-related damage is primarily mediated by M1 microglia (**Figure 2**).

MPO can form $HOCl/OCl^-$ in the presence of chloride ions and H_2O_2. These products are important substances that allow the body to resist microbial attacks (Babior, 1984; Nybo et al., 2019). However, excessive HOCl produced by the MPO-H_2O_2-Cl^- system in neutrophils and monocytes can damage various biological tissues, including the BBB (Klebanoff, 2005). Low-dose HOCl can trigger cell apoptosis, whereas high-dose HOCl can induce cell necrosis, including in neuronal cells and astrocytes, which are the main components of the BBB (Pullar et al., 2000; Whiteman et al., 2005). As a weak acid (acid dissociation constant [pKa] of 7.5) (Morris, 1966; Wei et al., 2020), HOCl-induced cellular acidosis is unlikely to be the cause of HOCl neurotoxicity. Recent studies have shown that the production of HOCl can activate an increase in the concentration of calpain. The activation of platelets can induce changes in platelet morphology. Similar to caspase-mediated cell apoptosis (Wolf et al., 1999), the activation of calpain can also rupture cell lysosomes (Yap et al., 2006), resulting in the robust occurrence of secondary injury in the central nervous system after stroke. BMVECs forms the morphological basis of the BBB through the formation of tight junction complexes (Swastika et al., 2019). Bernhart et al. (2018) showed that peripheral blood leukocytes produce HOCl through the MPO-H_2O_2-Cl^- system, which in turn produces chlorinated inflammatory mediators, such as 2-chlorohexadecanoic acid. 2-Chlorohexadecanoic acid can produce a lipid-toxic reaction in BMVECs, destroying the basic BBB structure, further aggravating secondary damage following stroke. Secondary injuries after stroke include hematoma expansion, perihematomal edema, and neurological deterioration (Castellazzi et al., 2010).

In addition to the direct and indirect destruction of the BBB by HOCl, MMPs are crucial for BBB destruction. MMPs are proteolytic, zinc-containing enzymes responsible for the degradation of the extracellular matrices surrounding the blood vessels and neurons in the central nervous system (Zhang and Kim, 2009; Fazal and Al-Ghoul, 2017; Yeo et al., 2020). The activation of MMPs can also induce tight junction degradation, leading to BBB breakdown following cerebral ischemia-reperfusion injury (Anctil et al., 2005; Nalamolu et al., 2020). Fu et al. (2001) showed that HOCl oxidizes the conversion of cysteine into thiol residues, which activates pro-MMP7. Studies showed that HOCl significantly enhanced the proteolytic activity of MMP8 and MMP9 (Weiss et al., 1985; Peppin and Weiss, 1986). Furthermore, after the 4-aminobenzoic acid amide-
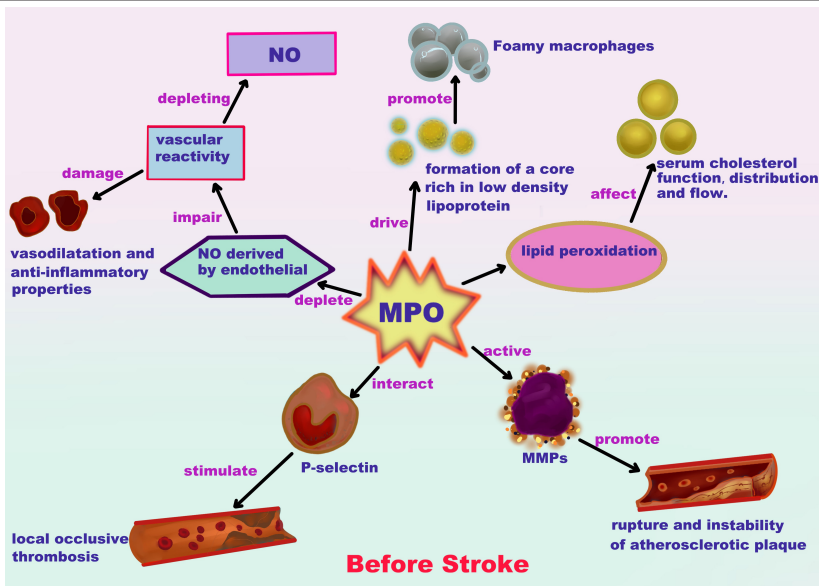
Figure 1 | Response caused by myeloperoxidase (MPO) in blood vessels before stroke.
MPO may promote stroke due to damage to the arterial wall through direct oxidation and indirect effects on blood vessel integrity and function, driving a core rich in low-density lipoprotein and promoting the formation of atherosclerotic plaques by foamy macrophages. These plaques affect the function, distribution, and flow of serum cholesterol due to lipid peroxidation. The activation of matrix metalloproteinases leads to atherosclerotic plaque rupture and instability, which can stimulate local occlusive thrombosis through P-selectin interactions. Depleting nitric oxide (NO) can impair vasodilation resistance against inflammation and impair vascular reactivity.
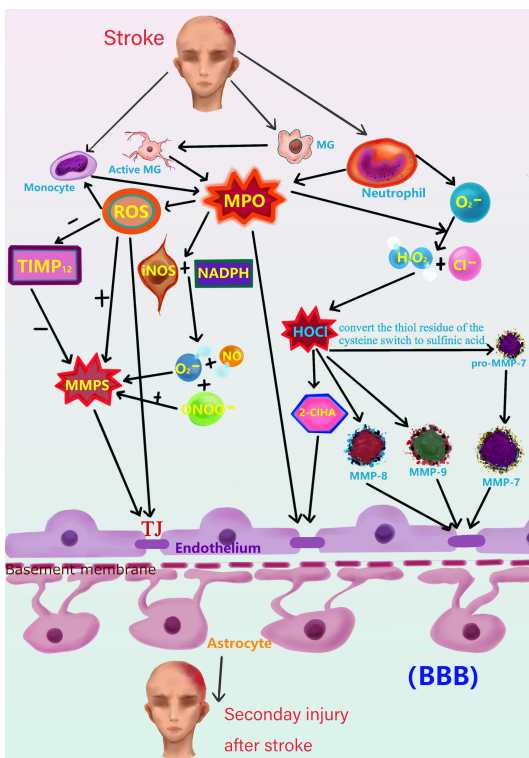

Figure 2 | Myeloperoxidase (MPO)-related cascade after stroke.
Active microglia, monocytes, and neutrophils produce MPO when a stroke occurs. In addition to direct damage to the BBB, MPO can cause indirect damage. After a stroke occurs, myeloid immune cells, such as monocytes, neutrophils, and microglia, produce MPO, which participates in the reaction between H_2O_2 and Cl^-, generating HOCl and activating MMP7, MMP8, MMP9, and other MMPs, further damaging the BBB. MPO may also induce the production of 2-ClHA, which further damages the BBB. MPO can increase the activity of ROS, which can directly attack the BBB. ROS can also enhance the activity of MMP and reduce the activity of TIMP12. The simultaneous effects of these positive and negative regulatory actions can activate MMPs to a greater extent. MPO can promote the production of O_2^- and NO by iNOS and NADPH. In addition to increasing MMP activity, MPO can produce $ONOO^-$, and $ONOO^-$ can further increase the activity of MMPs. This series of reactions will cause varying degrees of damage to the BBB, increasing the BBB permeability and aggravating secondary brain damage.
2-ClHA: 2-Chlorohexadecanoic acid; BBB: blood-brain barrier; Cl^-: chloride; H_2O_2: hydrogen peroxide; HOCl: oxidant chlorous acid; iNOS: inducible nitric oxide synthase; MG: microglia; NADPH: nicotinamide adenine dinucleotide phosphate; NO: nitric oxide; O_2^-: superoxide anion; $ONOO^-$: peroxynitrite ion; ROS: reactive oxygen species; TIMP12: tissue inhibitor of metalloproteinase 12; TJ: tight junction.

mediated inhibition of MPO, the expression of MMP9 was reduced (Kim et al., 2016). Therefore, HOCl can trigger molecular cascades that mediate the activation of MMPs, leading to BBB disruption. HOCl itself can also exacerbate oxidative stress, promote the translocation of p67(phox) and p47(phox), activating nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and mediating the production of superoxide, peroxynitrite, and oxidize endothelial NO synthase dimer in endothelial cells (Xu et al., 2006). Together, these compounds increase the damage to the central nervous system.

H_2O_2 is the final product of free oxygen radicals. Chloride ions act as a substrate for the catalytic reaction mediated by MPO, resulting in the formation of hypochlorous acid. The toxicity of hypochlorous acid is 50 times that of H_2O_2 (Graham et al., 2007). Therefore, excessive MPO increases the catalysis of H_2O_2 into hypochlorous acid, greatly enhancing cellular toxicity, especially in neuronal cells and astrocytes after stroke. In addition to these direct cytotoxic effects of MPO activity, elevated MPO activity increases reactive oxygen species (ROS) formation, MMP activation, and the production of inducible NO synthase, and inflammatory cytokines (i.e., IL-1β and tumor necrosis factor-α) (Ekdahl et al., 2003; Monje et al., 2003; Brovkovych et al., 2008; Cacci et al., 2008). These factors might cause indirect damage to neurons and astrocytes after stroke. ROS and MMPs can destroy tight junctions and disrupt the BBB, further aggravating stroke damage. Furthermore, MPO inhibition can reduce these inflammatory mediators (Monje et al., 2003; Cacci et al., 2008; El Kebir et al., 2008), indicating that MMPs act as downstream molecules during MPO-mediated inflammation (Fu et al., 2004; Cheng et al., 2018).

ROS avidly interact with large numbers of molecules, including other small inorganic molecules, as well as proteins, lipids, carbohydrates, and nucleic acids. Through such interactions, ROS may irreversibly destroy or alter the function of the target molecules. Consequently, ROS have been increasingly identified as major contributors to damage in biological organisms (Bedard and Krause, 2007; Diwanji and Bergmann, 2020). Related research has shown that ROS production increased BBB permeability and monocyte migration, and ROS activated MMP1, MMP2, and MMP9 (Haorah et al., 2007). The protein tyrosine kinase (PTK)-dependent pathway reduces the activity of tissue inhibitor of metalloproteinase 12, and increased MMP and PTK activity is closely related to the degradation of tight junctions in BMVEC proteins (Song et al., 2018). MMPs, PTKs, and antioxidant inhibitors can prevent monocyte migration, suggesting that oxidative stress causes BBB damage through the activation of MMPs and the PTK-mediated degradation of BMVEC proteins (Haorah et al., 2007). NADPH and inducible NO synthase produce superoxide anion (O_2^-) and NO after stroke, which in turn produce peroxynitrite ion ($ONOO^-$) and further produces factors that increase the activity of MMPs (Chen et al., 2016), which destroy tight junctions and the BBB (Gu et al., 2011). NADPH oxidase is a very important pro-oxidase that induces superoxide anion (O_2^-) and H_2O_2 and is a significant source of ROS (Bedard and Krause, 2007). Free radicals play an important role in cerebral ischemia/reperfusion injury. The accumulation of toxic free radicals, such as ROS and reactive nitrogen, increases brain

tissue susceptibility to ischemic injury and triggers various molecular cascades, resulting in increased BBB permeability, brain edema, bleeding, inflammation, and neuronal death. Furthermore, free radicals can activate MMPs, which is a critical step in damaging the BBB (**Figure 2**).

The inflammatory response and oxidative stress both damage the BBB and disrupt neurogenesis. Disorders of learning, language memory, and execution ability are most likely to occur after a stroke, primarily due to damage in corresponding brain areas, such as the cerebral cortex and hippocampus. Functional damage to these brain areas occurs due to repeated ischemia and inflammatory infiltration, which gradually reduces the recruitment of stem cells, affecting neurogenesis (Lin et al., 2018; Deng et al., 2021).

Potential of Myeloperoxidase in Stroke

The genetic risk and predictive value of MPO in stroke

The genetic contributions of MPO levels to ischemic stroke and recurrent stroke risk have been demonstrated in all races (Liu et al., 2012). More specifically, the high expression of MPO-related genes may increase the susceptibility to stroke. Manso et al. (2011) analyzed differences in the expression levels of MPO-related genes between a stroke group and a control group and found a positive correlation between the rs8178406 sequence in the MPO gene and stroke occurrence, providing the additional evidence that MPO is involved in stroke susceptibility and demonstrating a significant correlation between the MPO gene and stroke occurrence. Furthermore, the high expression of MPO protein also increases the risk of stroke, which has been confirmed by other studies (Palm et al., 2018; Pravalika et al., 2019; Ramachandra et al., 2020). Another study from Phuah et al. (2017) examined a large sample cohort that included 1409 cases of primary intracerebral hemorrhage from three studies; a cohort containing 1624 controls and 12,577 ischemic stroke patients from the NINDSSiGN study; an expanded cohort of 25,643 controls; METASTROKE Constatium's 10,307 ischemic stroke cases; and a validation cohort of 29,326 controls. The results revealed that genetic determinants of elevated MPO levels and the risk of primary intracerebral hemorrhage (odds ratio 1.07, P = 0.04) were associated with the risk of recurrent intracerebral hemorrhage (hazard ratio 1.45, P = 0.006). In the analysis of ischemic stroke subtypes, MPO with increased genetic risk score was only closely related to the cavity subtype (odds ratio 1.05, P = 0.0012). These results suggest that increased genetic variations in MPO levels increased the risk of primary intracerebral hemorrhage and lacunar stroke, proving that MPO is correlated with the risk of small vessel stroke (Phuah et al., 2017).

High expression of the MPO gene can increase the risk of stroke. Simultaneously, MPO plays an important inflammatory role. The effects of a lack or low expression of the MPO gene were examined by Lanza (1998), who indicated that the lack of MPO does not significantly impact human life. Although MPO is an important molecule produced by neutrophils and is involved in the killing of certain microorganisms, no data or research has shown that a lack of MPO results in increased susceptibility to severe or persistent infections. Although serious infections occasionally occur in patients with MPO deficiency, these affect fewer than 5% of patients with MPO deficiency, indicating a low incidence (Kitahara et al., 1981). Visceral candida infections have been reported in patients with MPO deficiency; however, Stendahl et al. (1984) have shown that the microbicidal and fungicidal activities of MPO-deficient neutrophils are only slightly weakened compared with normal neutrophils. Some studies have shown that MPO-deficient neutrophils have prolonged respiratory bursts, resulting in increased H_2O_2 production in response to stimulation. These factors may compensate for the lack of peroxidase (Cramer et al., 1982). Therefore, on the basis of research performed in MPO knockout models, further relevant research can be performed to observe bodily changes in response to the loss of MPO production, to determine whether the MPO blockade will cause serious damage to the body. Such research should also seek to observe changes in the physiological regulation mechanisms mediated by MPO. If MPO knockout or knockdown shows little effect on the body, MPO inhibition could be applied to animal models of stroke to determine the therapeutic effects of MPO inhibition.

MPO as a therapeutic target in stroke

Malle et al. (2007) found that MPO can be used as a target for future drug development. Related drugs inhibit MPO activity and inhibit substrate production by combining halide binding sites with

an aromatic substrate or inhibitor binding sites. They included 4-aminobenzoic acid amide, N-phenylacetamide, and melatonin (Malle et al., 2007).

On the basis of the hypothesis that MPO targets can be used as drugs, many animal experiments have been performed to examine the application of MPO inhibitors to stroke models in recent years. The classic MPO-specific inhibitor, 4-aminobenzoic acid amide, is a common drug used in stroke treatment research, and neurogenesis following ischemic stroke increased after 4-aminobenzoic acid amide treatment. The inhibition of MPO also increased the levels of brain-derived neurotrophic factor, phosphorylated C-reactive protein, acetylated H3 receptor, Cys-X-Cys receptor 4, and neuronal core antigen and reduced inflammatory cell infiltration mediated by MMP9. These results underscore the detrimental role of MPO activity in post-ischemia neurogenesis. A series of experiments demonstrated that MPO activity is inversely proportional to neurogenesis after stroke, and the inhibition of MPO activity increases cell proliferation and improves neurogenesis after ischemic stroke (Drexelius et al., 2019; Kim et al., 2019; Qiu et al., 2021). They further found that the protective environment induced by MPO inhibition or the knockout of MPO genes can reduce inflammatory cell aggregation and increase survival factors, which can improve stroke outcomes. MPO inhibition may represent a promising therapeutic target for stroke therapy, possibly even days after the stroke has occurred (Kim et al., 2016).

New MPO inhibitors are being discovered continuously. For example, N-acetyl lysyl-tyrosyl cysteine amide can inhibit the activity of MPO, which can reduce the numbers of M1 microglia and N1 neutrophils in the brains of stroke mouse models, protecting neuronal function (Yu et al., 2018). Many drugs can also exert antioxidant and anti-inflammatory effects and inhibit MPO. For example, in the study of ischemic stroke, after using rosmarinic acid (Fonteles et al., 2016), melatonin (Pei and Cheung, 2004), tropisetron (Daneshmand et al., 2011), and the traditional Chinese medicine extract Leonurus heterophyllus (Liang et al., 2011), a significant decrease in the amount and activity of MPO was observed. Importantly, cerebral infarction and neuronal damage were improved. Another example is in the study of hemorrhagic stroke. Lee et al. (2006) induced cerebral hemorrhage by injecting collagenase into the rat basal ganglia and administered memantine to inhibit inflammation. They found that the number of MPO-positive cells around the hematoma was significantly reduced in the memantine-treated group, which induced functional recovery after cerebral hemorrhage (Lee et al., 2006).

Although no MPO inhibitors are currently approved for use in clinical stroke patients, many preclinical candidate drugs are under development, and one candidate drug has completed Phase IIa clinical trials (Churg et al., 2012; Forbes et al., 2013; Ward et al., 2013). On the basis of the above review, MPO plays a vital role in stroke occurrence and development. After MPO inhibition, neurogenesis becomes active, and stroke recovery improves; therefore, MPO is expected to become a new target for stroke treatment.

Conclusions

MPO leads to a significant increase in stroke occurrence and development. The overexpression of MPO typically results in impaired BBB permeability. For patients with congenital or acquired loss of MPO expression, the effects on their immunity are not significant. Therefore, MPO can be targeted clinically for stroke treatment and potentially other inflammation-related diseases. Currently, no MPO inhibitors have been approved for clinical use, and the most commonly used specific inhibitor of MPO, ABAH, has a strong toxic effect on the human body. Many other inhibitors, including those mentioned in our article, are not specific inhibitors, and few studies have been performed on these inhibitors, none of which have reached the level of clinical trial. Whether these non-specific inhibitors have side effects on the human body remains unclear. The specific damage mechanism of MPO also remains unclear, and more research is necessary to clarify the underlying mechanisms. The specific etiological mechanism that leads to the activation of MPO during the occurrence and development of stroke also requires further clarification. Neutrophils are a key source of MPO production, and central immune cells can also produce MPO. Additional MPO-targeting drugs that are safe for clinical use must be developed.

Review

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