Bioactive Materials 11 (2022) 140–153

Contents lists available at ScienceDirect

Bioactive Materials

journal homepage: www.keaipublishing.com/en/journals/bioactive-materials

Current status and outlook of biodegradable metals in neuroscience and their potential applications as cerebral vascular stent materials

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ARTICLE INFO

Keywords:
Biodegradable metals
Neuroscience
Mg alloys
Brain stents
Ischemic stroke

ABSTRACT

Over the past two decades, biodegradable metals (BMs) have emerged as promising materials to fabricate temporary biomedical devices, with the purpose of avoiding potential side effects of permanent implants. In this review, we first surveyed the current status of BMs in neuroscience, and briefly summarized the representative stents for treating vascular stenosis. Then, inspired by the convincing clinical evidence on the *in vivo* safety of Mg alloys as cardiovascular stents, we analyzed the possibility of producing biodegradable cerebrovascular Mg alloy stents for treating ischemic stroke. For these novel applications, some key factors should also be considered in designing BM brain stents, including the anatomic features of the cerebral vasculature, hemodynamic influences, neuro-cytocompatibility and selection of alloying elements. This work may provide insights into the future design and fabrication of BM neurological devices, especially for brain stents.

1. Introduction

Biodegradable metals (BMs), represented by magnesium-, zinc-, and iron-based alloys, are expected to degrade or corrode gradually *in vivo* after performing their supportive assisting functions during tissue healing or disease diagnosis, under the influence of appropriate host responses. Compared with their polymeric counterparts, BMs possess higher mechanical strength and show better performance as cardiovascular stents and bone implants [1–3]. Several reviews have presented the state-of-the-art technologies in developing BMs-based degradable biomedical implants [4–7]. However, their application in neuroscience is still in its infancy.

Cerebrovascular disease is the leading cause of death in China and the 2nd leading cause of death globally, exerting a heavy burden on public health [8]. Their primary pathologies include the obstruction or rupture of brain blood vessels, which leads to ischemic or hemorrhagic stroke, respectively. In addition to traditional drug therapies, the neuro-interventional approach for cerebrovascular disease treatment is much more effective with improved outcomes [9]. Existing endovascular devices include coils, stents, flow diverters, and stent retrievers [10], which are mainly made of NiTi alloys, Co alloys or 316 L stainless steel, with good biomechanical compatibility for brain vessels and cytocompatibility for nerve cells. However, the constant presence of an inherent non-degradable metallic stent can impair vasomotor response and induce a prolonged inflammatory reaction and thrombosis [11]. In addition, the required dual anti-platelet therapy may increase

Peer review under responsibility of KeAi Communications Co., Ltd.
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https://doi.org/10.1016/j.bioactmat.2021.09.025
Received 11 July 2021; Received in revised form 1 September 2021; Accepted 18 September 2021
Available online 11 October 2021

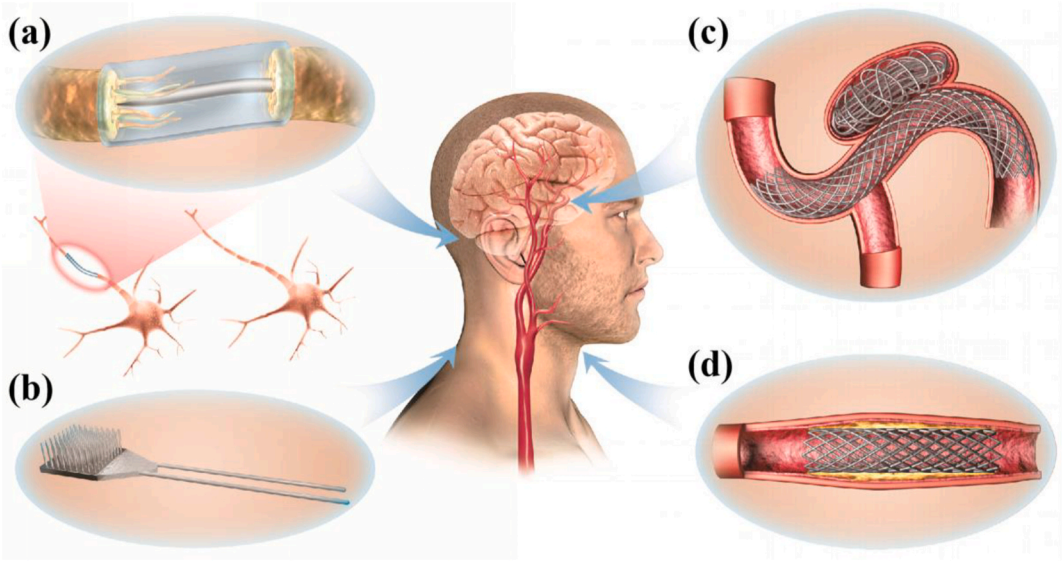

Fig. 1. The application of Mg-based alloys in neuroscience. Mg alloys can be fabricated as filaments within: (a) nerve conduits to accelerate nerve regeneration [32, 33], (b) nerve electrode and devices for neural recording and monitoring [34–36], (c) coiling-assisted stents for cerebrovascular aneurysms [37], and (d) expanded endovascular stents for the occlusion common carotid artery (CCA) [38].

intracranial bleeding risks. In the scenario of cardiovascular stenosis, the biodegradable stent is developed to tackle those side effects, which is considered to be the fourth revolution in interventional cardiology [12]. When it comes to cerebrovascular disease treatment, is it possible to make biodegradable metallic endovascular devices? Before answering this question, an overview of the use of BMs in neuroscience as well as their application in cardiology is critical.

Currently, with the development of biodegradable materials, novel biodegradable brain implants are fabricated, such as intracranial electronic sensors [13], wireless drug delivery device for brain tumors [14], optical sensors for pressure and temperature monitoring [15] and electrode array for electrophysiological recording [16]. Early efforts on making these bioresorbable devices were focused on biodegradable polymers and subsequently on silicon-based semiconductors [17,18]. The application of BMs in neuroscience is still in its infancy, and some of the BMs have only been exploited as device substrates for brain implants in the form of thin foils [19].

In this review, we first surveyed the current research of BMs in neuroscience, and briefly summarized the representative stents for vascular stenosis treatment. Then we explored the possibility to produce biodegradable cerebrovascular Mg alloy stents for ischemic stroke treatment and discussed some key factors that should also be considered in designing BMs brain stents, including anatomic features of the cerebral vasculature, hemodynamic influences, neuro-cytocompatibility and selection of alloying elements.

2. Application of BMs in neuroscience

Biodegradable medical devices are limited mostly to orthopedic/cardiovascular implants or surgical sutures. Representative Mg-based, Fe-based, and Zn-based BMs have been thoroughly reviewed with emphases on their physiochemical and corrosion properties, *in vitro* and *in vivo* biocompatibilities, as well as various techniques to manipulate the biodegradable behaviors [20–24]. These translational research on BM have shown their potential application in neuroscience.

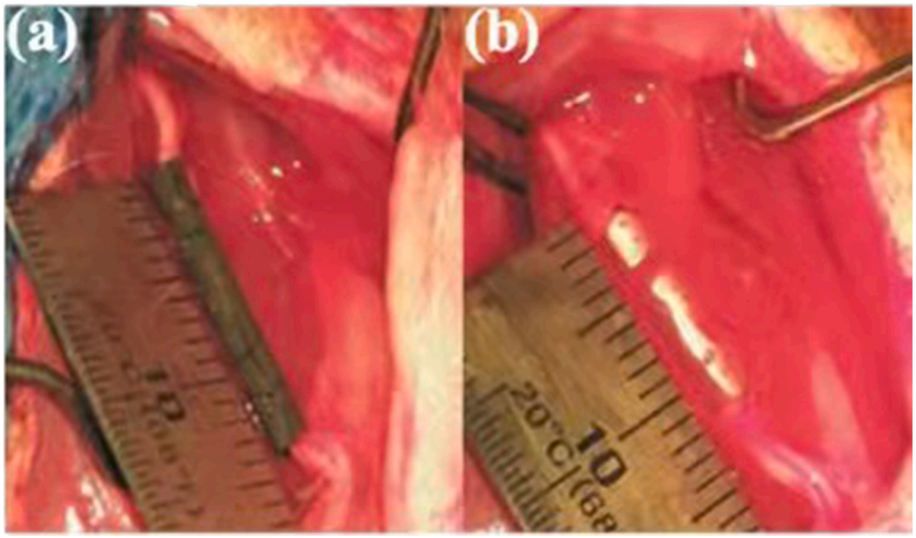

Fig. 2. Photos of nerve conduits implantation: (a) HA-WE43 (hydroxyapatite-coated Mg alloy) nerve conduit and (b) silicone nerve conduit [43].

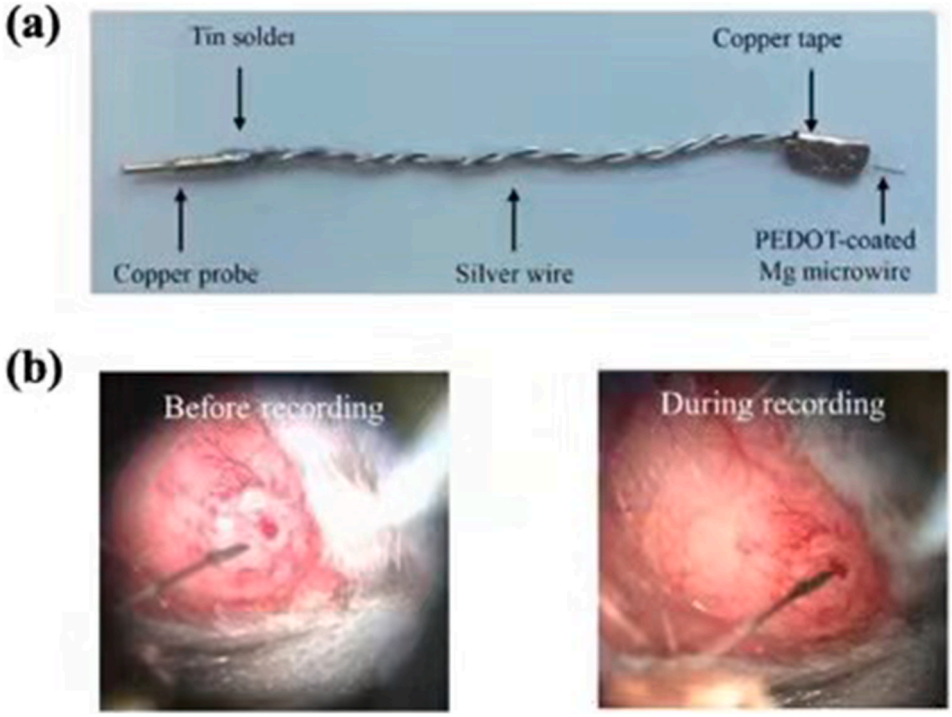

Fig. 3. (a) Mg microwire as working electrode with PEDOT coating and being attached to silver wire by copper tape; (b) Microscopic image of surface-modified Mg microwire before recording and during recording [48,49].

2.1. Magnesium alloys

Since magnesium (Mg) and its alloys have tunable mechanical strength, and proper biodegradability, which can be further regulated by surface coating techniques [25], they are considered a promising alternative to permanent biomedical materials [26].

Besides, Mg ion can be used as a neuroprotective agent, which has been verified in several animal/clinical studies of cerebral ischemia treatment [27–31]. However, there is little research on the interactions between Mg alloys and brain tissue. Only several reports are available regarding their applications in neuroscience and neurosurgery (Fig. 1).

2.1.1. Nerve repair and regeneration

Nerve repair and regeneration is a big clinical challenge, especially for nerve defects longer than 2–4 cm [39]. Currently, drugs or growth factors are decorated onto or incorporated into various lipids, polymers, metals and carbon materials to support nerve function recovery. Compared with polymers, the use of biodegradable magnesium wires in nerve conduits will accelerate peripheral nerve regeneration across the injury gap [40], and the Mg filament implants degraded completely without evidence of scarring [41]. The Mg-based metallic glasses ($Mg_{70}Zn_{26}Ca_4$) are also studied and proposed to be a promising material to make implantable nervous prosthetic devices [39]. Moreover, the Mg-based alloy (Mg–2Zn–Nd and Mg–10Li) extracts showed no neural toxicity compared to control groups [42]. Typical nerve conduits implantation photos are shown in Fig. 2. HA-WE43 nerve conduit were in implanted over the sciatic nerve gap and showed controlled degradation and absence of gas formation around the regenerated neural tissue after

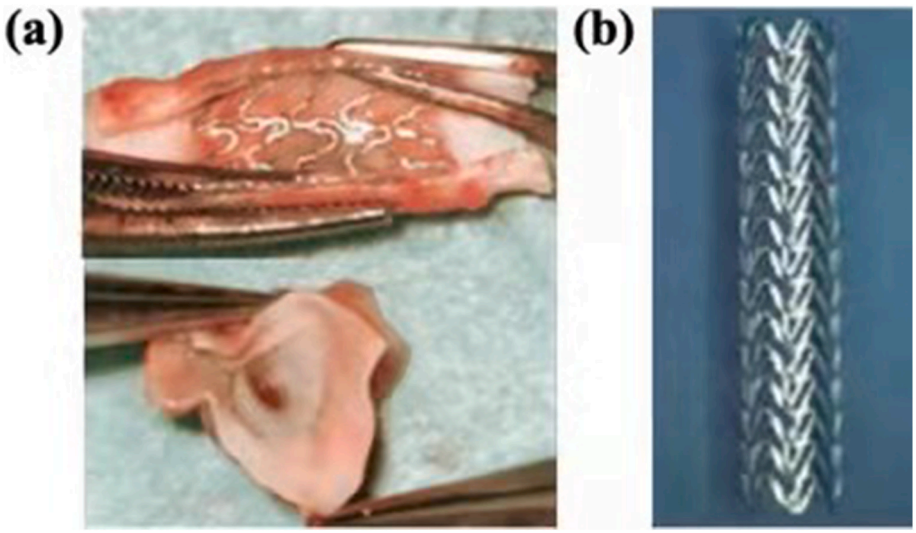

Fig. 4. (a) BMs stents assisted coiling for aneurysm [37]; (b) BMs carotid artery stents forvascular occlusion and stenosis [53].

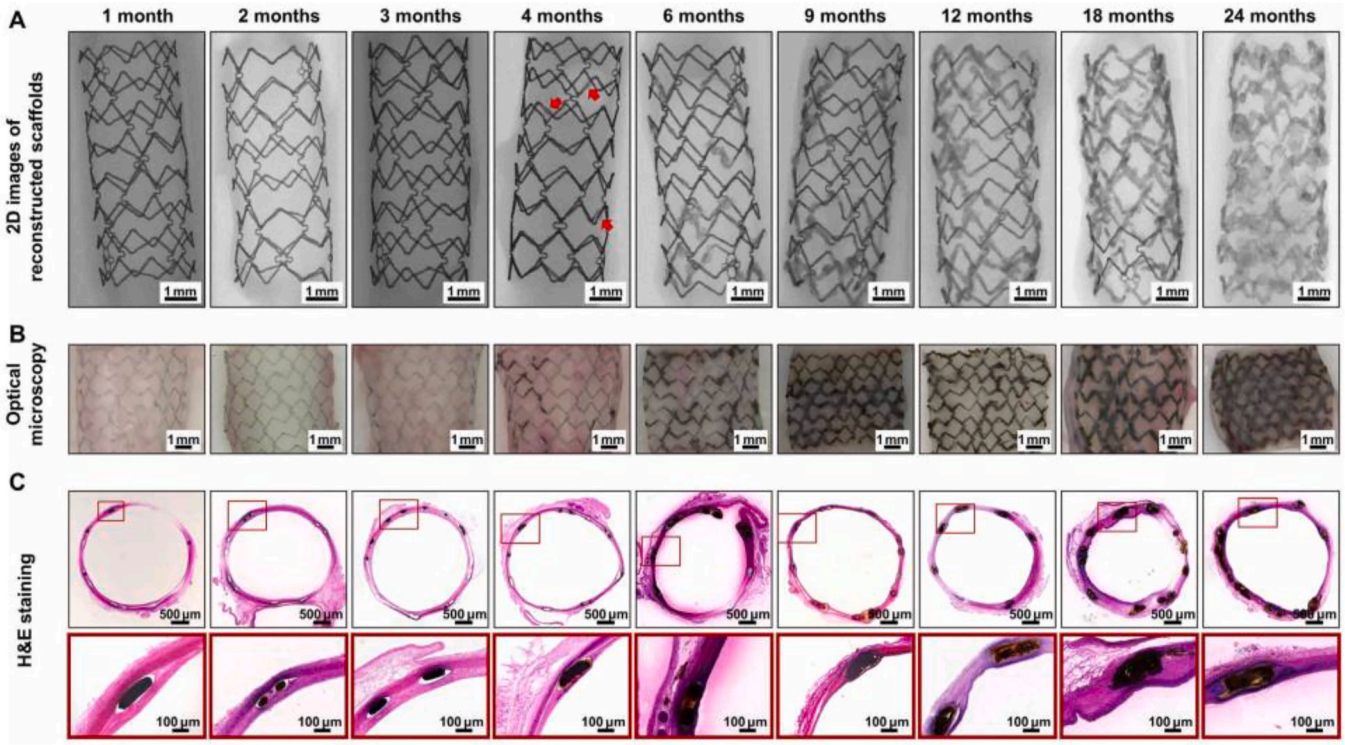

Fig. 5. *In vivo* degradation behavior of the PDLLA-Zn-nitrided Fe BRS in rabbit abdominal aortas at different time points after implantation [65].

12 weeks post-surgery [43].

2.1.2. Nerve electrode

The electrical properties and signal pathways of neurons can provide significant insights into the discoveries of new treatment methods for neurological diseases [44,45]. However, the permanent presence of the rigid electrode can induce a mechanical mismatch with soft brain tissues, which is an obstacle to successful long-term implantation [44]. As an alternative, biodegradable polymers, such as silk fibroin, polyvinyl alcohol (PVA) and polylactic acid-glycolic acid (PLGA), are exploited to make biodegradable electronic devices, but they performed poor mechanical properties [46,47]. As shown in Fig. 3, implantable Mg-based electrode was firstly fabricated by Liu et al. for neural recording and stimulation and this micro-electrode was coated by poly-3, 4-ethylenedioxythiophene (PEDOT) using electrochemical deposition technique [48,49] with excellent neural-recording capability and *in vivo* stability in the auditory cortex of a mouse [49].

2.1.3. Vascular stents

Commercially available cerebrovascular stents are made of non-degradable metals [9], and their long-term existence may lead to acute thrombosis formation or late in-stent restenosis [50,51]. To address those problems, biodegradable stents are proposed and designed to disappear after fulfilling their mission. An ideal degradable stent needs to meet both the requirements of mechanical and degradable properties, and a low degradation rate within the first 6–12 months after implantation in order to ensure the success of blood vessel remodeling. Then, the stent should degrade at an appropriate corrosion rate within 12–24 months without causing any side effects.

At present, BMs cerebral vascular stents have been explored in the treatment of carotid artery stenosis and aneurysm (Fig. 4). The ruptured intracranial aneurysm can lead to a high mortality rate and poor neurological outcomes in patients. Intracranial stents are introduced together with endovascular coils to tackle this problem. Mg stent was implanted into a rat model for the treatment of saccular aneurysms (Fig. 4a) [37]. In addition, *Wang* et al. evaluated the biological outcomes of polytetrafluoroethylene membrane coated Mg-Nd-Zn-Zr alloy stent for the treatment of occlusion of a lateral aneurysm model in the rabbit common carotid artery (CCA). Their study suggested that the mean diameter and mean vessel area of CCAs at 6 months and one year after stents implantation were significantly greater than those treated with Co–Cr stents [38]. Also, *Grüter* et al. implanted Mg alloy stent into a sidewall aneurysm model and found no formation of late in-stent stenosis within 6 months and no negative interaction between the platinum coil and Mg alloy stent [52]. For carotid artery stenosis, *Zhang* et al. implanted a bare Mg-Nd-Zn-Zr (JDBM) stent into the CCA of New Zealand rabbits. Completed re-endothelialization of the stents was observed within 28 days and most of the JDBM stent struts were replaced by degradation products *in situ* within 4 months (Fig. 4b) [53].

2.2. Iron alloys

Iron is an important cofactor in metabolism and is featured as the most abundant transition metal element in the brain [54]. The elevated iron level in cerebrospinal fluid is associated with Alzheimer's disease pathogenesis [55]. And iron oxide nanoparticles have been used in the diagnosis and treatment of neurodegenerative diseases as imaging agents and drug delivery vehicles [56]. Biodegradable iron-based alloys have been investigated as bone replacement material [57], urinary implant material [58] and cardiovascular stent [59].

The *in vivo* safety of Iron stents (>99.8% iron) was initially verified in 2001 by implantation into rabbit's aortas [60], and most of the research thereafter are mainly focused on animal studies [61]. In a preclinical investigation, the first ultrathin (~70 mm) sirolimus-eluting iron stent (Lifetech Scientific, Shenzhen, Guangdong, China) was implanted in porcine coronary arteries and exhibited comparable results with the cobalt-chromium everolimus-eluting stent (XIENCE Prime stent, Abbott Vascular, USA) [62]. The corrosion rate of the iron substrate can be increased by polylactide (PLA) coating due to its acidic degradation product [63], and the stent could provide effective local drug delivery to the target area. The preclinical result showed no significant difference in the area of stenosis compared to XIENCE stent up to 6 months while

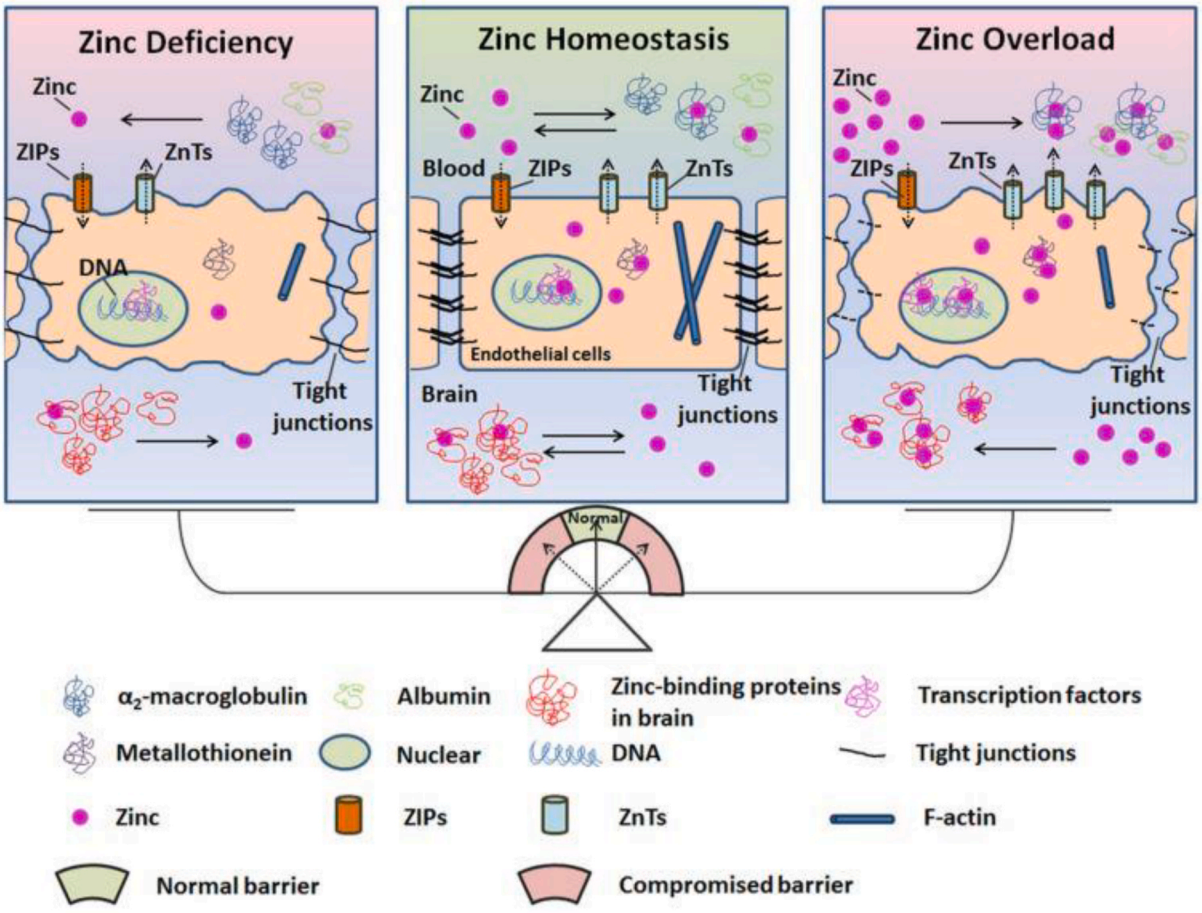

Fig. 6. Schematic diagram of the role of zinc homeostasis in the normal function of the blood-brain barrier [67].

stent thrombosis was observed during the study [62,64]. A recent *in vivo* study in both rabbit abdominal aortas and human coronary arteries suggested that the PDLLA-Zn-nitrided Fe stents degraded completely after 24 months post implantation. Their biodegradation process is shown in Fig. 5. The surface-modified Fe stents remained intact within the early two months implantation; some corrosion products were observed after 4 months implantation [65].

Although iron-based biodegradable stent is a competitive and promising candidate as a temporary scaffold, a literature review from Dr. Scarcello [61] claims that the biocompatibility of iron alloys has not been well understood and it is not ready to classify iron or iron-based alloys as biocompatible materials. Recently, a fully biodegradable device for nerve regeneration was produced by using iron-manganese alloy as water-soluble electrodes [66]. The application of iron-based alloys in neuroscience is rarely reported. This may be due to the local toxicity on nerve cells, which has not been studied in depth, especially regarding endothelial dysfunction, oxidative stress, carcinogenicity or genotoxicity [61].

2.3. Zinc alloys

Zinc ions play significant roles in neurogenesis and synaptic activities [67] and serve as important cofactors in all six enzyme classes [68]. High zinc levels *in vivo* can induce focal neuronal pathology and zinc deficiency can give rise to mental lethargy [69]. Interrupting the zinc/blood-brain barrier (BBB) system will damage the microenvironment in the brain, leading to pathological diseases. The serum zinc level maybe an independent risk factor for ischemic stroke patients [70]. As it is illustrated in Fig. 6, zinc may serve as a potential target for protecting the BBB in stroke patients, and reducing hemorrhage transformation, inflammation and edema [67].

In terms of zinc-based alloys, their acceptable biodegradability and reasonable biocompatibility have made them a promising BM for both vascular and orthopedic applications [71–73]. In 2017, *Zheng* et al. implanted pure zinc stents into the abdominal aorta of rabbits for 12 months and these stents maintained mechanical integrity for 6 months with 41.75 ± 29.72% of stent volume degraded after 12 months implantation without severe inflammation, platelet aggregation, thrombosis formation or obvious intimal hyperplasia (Fig. 7) [74]. In addition, a novel biodegradable Zn-0.8Cu stent was fabricated and implanted into porcine coronary arteries for up to 24 months and the result showed that it provided sufficient structural support and exhibited an appropriate degradation rate without degradation product accumulation, thrombosis, or inflammatory responses [3]. In addition, the Zn–Cu stent exhibited an antibacterial effect against *S. aureus* [75].

Zn-based alloys as the third generation stent material could be a promising candidate for stent applications due to their reliable and tunable strength and ductility, and acceptable biocompatibility [76,77]. The stents from Zn alloys can present thinner struts and better reinflation ability, with lower strength and creep resistance than that of Fe alloys [22]. The corrosion current density of Zn is higher than that of Fe, but lower than that of Mg [78]. Besides, compared with Zn alloys, the degradation of Mg alloys is accompanied by H_2 evolution leading to high risk of gas embolism [79]. And the functional performance of these biomedical alloys can be improved by alloying proper elements and surface modifications. However, the research on zinc alloy cardiovascular degradable stent is still in its infancy. Besides, there are few studies about the application of zinc alloys in neuroscience, which may be due

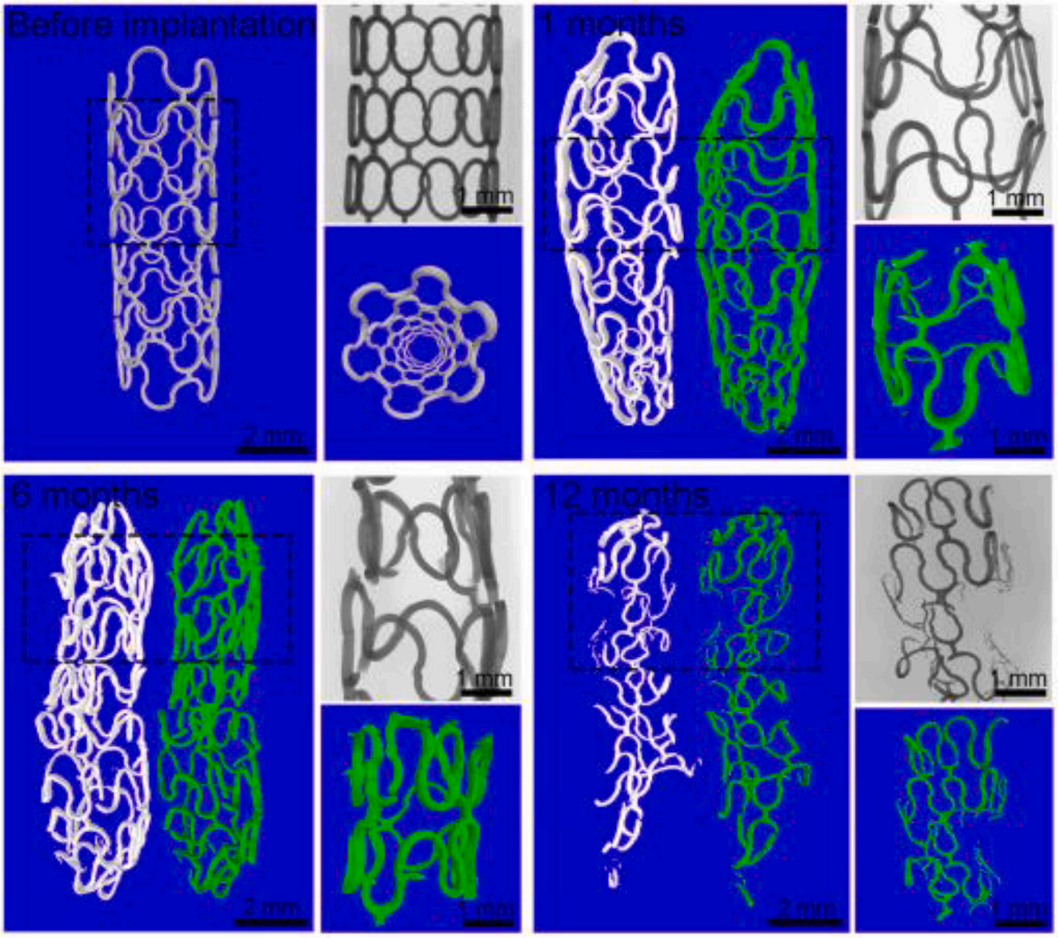

Fig. 7. The 2D and 3D micro-CT images of zinc stents after 0, 1, 6 and 12 months implantation in the aorta of rabbits from Ref. [74].

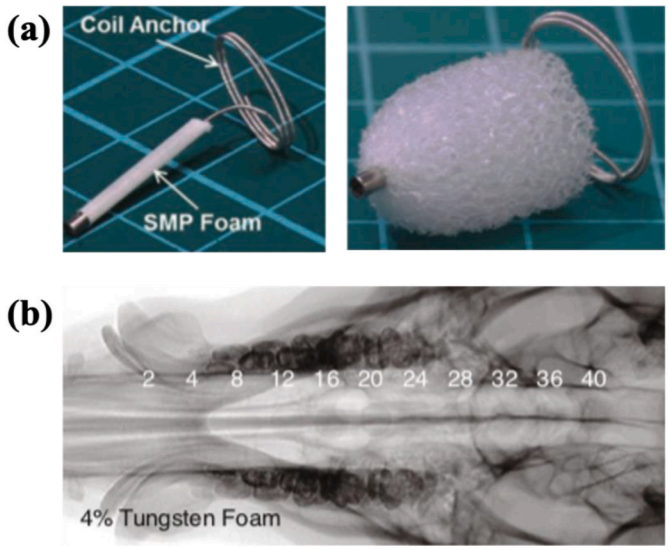

Fig. 8. (a) Shape-memory polymers (SMPs) device before and after expansion [80]. (b) The 4% tungsten-doped SMP foam device with increasing thicknesses from 2 to 40 mm imaged via fluoroscopy with a pig's skull thickness [81].

to the sensitivity of nerve cells to high concentrations of zinc ions [67].

2.4. Tungsten

Tungsten (W) has been investigated as embolization coils in intracranial aneurysms with *in vivo* degradability [80]. Shape-memory polymers (SMPs) foams can be rendered radiopaque with doped tantalum or tungsten for a simulated aneurysm model (Fig. 8) [81]. The implantation of W coils (SPI, Balt, France) into the subclavian artery of New Zealand white rabbits led to a significant increase in serum W levels four months after the surgery [82]. This versatile metal was also exploited to make microwire electrodes for neural activity recording [83]. Patrick et al. reported that the corrosion rate of W microwires in 0.9% phosphate buffered saline was 300–70 μm/yr [83].

2.5. Molybdenum

Molybdenum (Mo) was usually selected as an alloying element to make Ti–Mo alloys and Co–Cr–Mo alloys for manufacturing surgical implants [84]. In 2020, Redlich et al. explored the corrosion behavior of commercially high-purity molybdenum in simulated physiological salt solutions and stated that molybdenum could be a potential novel biodegradable material for stent fabrication [85]. Besides, Kang et al. invented a bioresorbable silicon electronic cerebral sensor by using Mo wires as an interface to the wireless module and depositing Mo foils as interconnects (Fig. 9) [13]. Combined with poly(l-lactide) and polycaprolactone composite, Mo was also used by Zhao et al. to fabricate a bioresorbable electrode array for brain monitoring [86].

To summarize, the applications of BMs in the neuroscience are

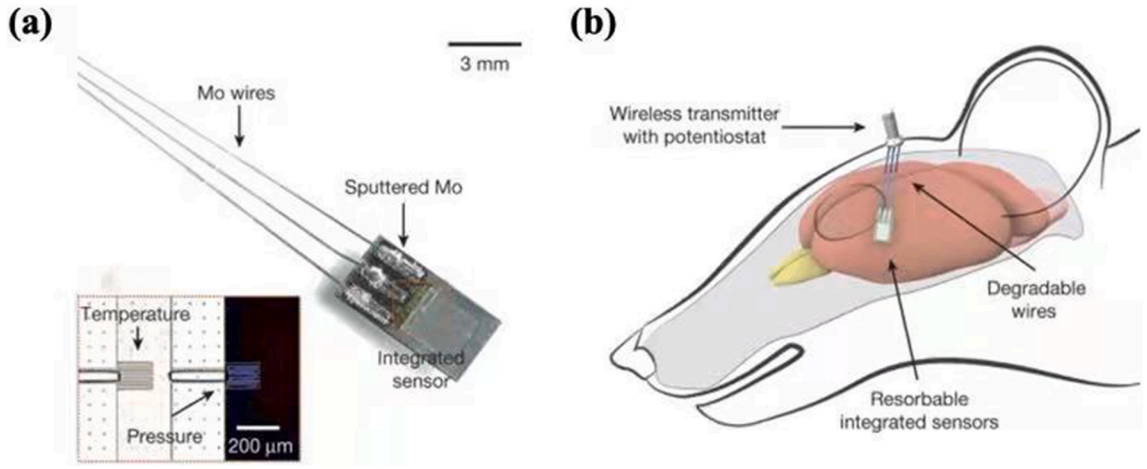

Fig. 9. Image of bioresorbable pressure and temperature sensors integrated with dissolvable metal interconnects (sputtered Mo, 2 μm thick) (a) and wires (Mo, 10 μm thick) (b) [13].

mainly divided into two categories. One of the applications was based on the mechanical properties of metal to develop vascular stents, and the other can be as core components of electronic devices for neural implantations and stimulations due to the conductive properties of metal. Molybdenum and tungsten are refractory and rare metals, which have the disadvantage of great difficulty in processing. Due to the uncertainty of the biocompatibility of iron and zinc ions in nerve cells, further studies of Fe-based and Zn-based alloys in neuroscience are limited. Compared with other metals, Mg-based alloys have a stable degradation rate and good biocompatibility, which shows a promising application in neuroscience [37,38].

3. From BM cardiovascular stents to cerebrovascular stents

Cardiovascular stents have been studied for nearly 30 years, from the initial non-degradable bare-metal stents to the drug-eluting stents, and then to biodegradable stents. Representative and commercially available stents for cardiovascular and cerebral vascular stenosis treatment are shown in Fig. 10.

The biodegradable cardiovascular polymer stents are promising [100], but have the drawbacks of weak mechanical strength and thick stent strut thickness [101,102]. The elastic modulus of polymers (such as poly-L-lactic acid, polyethylene terepthalate, and poly-L-glycolic acid PLGA [103]) ranges from 1 to 5 GPa [104], which cannot confer ideal mechanical properties for stent fabrication and result in early recoil of the stent [105]. Besides, the increased strut thickness and high crossing profile can disturb the laminar blood flow and lead to difficulties in stent deliverability, especially in the use of tortuous cerebral vasculature [105].

In recent years, the research focus of biodegradable cardiovascular stents is gradually turning to the ones made of BMs, such as iron alloys, magnesium alloys, zinc alloys [106,107]. Among them, Mg alloy bioresorbable devices are much more widely studied [23] because of their superior biocompatibility and biodegradability [108]. As shown in Table 1, compared with Mg alloys, the *in vivo* studies of iron and zinc alloys are mainly focused on *in vivo* animal studies (including rat, rabbit, porcine and sheep models), and clinical investigations on their safety as cardiovascular stents are still in early stage. And their applications in neurological areas as biomedical devices are few. In Fig. 10, most of the brain stents are made of NiTi alloys without degradable properties.

In 2013, the first clinical trial (BIOSOLVE-1) of the drug-eluting Mg alloy stents (DREAMS 1G) was conducted [137] and after that, in 2016, another human trial of Mg-based stent (DREAMS 2G) was reported [138]. Compared with DREAMS 1G, the DREAMS 2G displayed a more stable corrosion rate and better clinical performances. The related stent information is shown in Table 2.

Except for their usage as heart stents, Mg alloys can also be manufactured into devices for intraluminal tracheal stenosis treatment [140], bone repair and regeneration [140], vascular clamps and cervical spine interbody fusion [141].

Learning from the idea of BM cardiovascular stents and based on the thorough research of Mg alloys as heart stents and their application in neuroscience, we will explore the possibility of producing biodegradable cerebrovascular Mg alloy stents for ischemic cerebrovascular stenosis treatment.

4. Prospective BM cerebrovascular stents: Mg alloy stents

Ischemic strokes account for around 85% of total stroke patients [142]. Except for standard pharmacological and mechanical thrombolysis approaches, endovascular revascularization with the use of stents has been increasingly accepted for ischemic cerebrovascular disease treatment [143]. Mg alloys are chosen as a potential candidate to make brain stents and some key factors should be considered in designing it.

4.1. Cerebral vasculature

Compared with cardiovascular vessels, the cerebral vasculature is very tortuous, and the diameter of some intracranial arteries is only several millimeters. The intracranial arteries do not have an external elastic lamina and lack supporting perivascular tissue with reduced wall thickness (lumen diameter ratio), which makes the cerebral arteries susceptible to rupture under hemodynamic loads [144,145]. When a stent is implanted, it can induce alterations in the mechanical stimuli on the vascular walls, resulting in the formation and progression of in-stent restenosis [146]. Moreover, the level of restenosis is related to the level of implantation-induced vascular injury [147]. Therefore, flexibility is the first consideration when making a new cerebral stent [9]. The bending behavior of BM cerebrovascular stents as the primary factor due to the cerebrovascular curvature should be investigated to avoid the high-stress zone of the bridge as well as the inner-stent protrusion phenomenon in the bending state [148]. And it is of significant importance to ensure the biomechanical compatibility between a stent and an artery by optimizing the stent geometries by many methods, for example, by changing the location of the connection point between rings and links of stents to achieve tunable Poisson's ratio [149] and by using multi-objective optimization based on finite element analysis to improve stent flexibility [150].

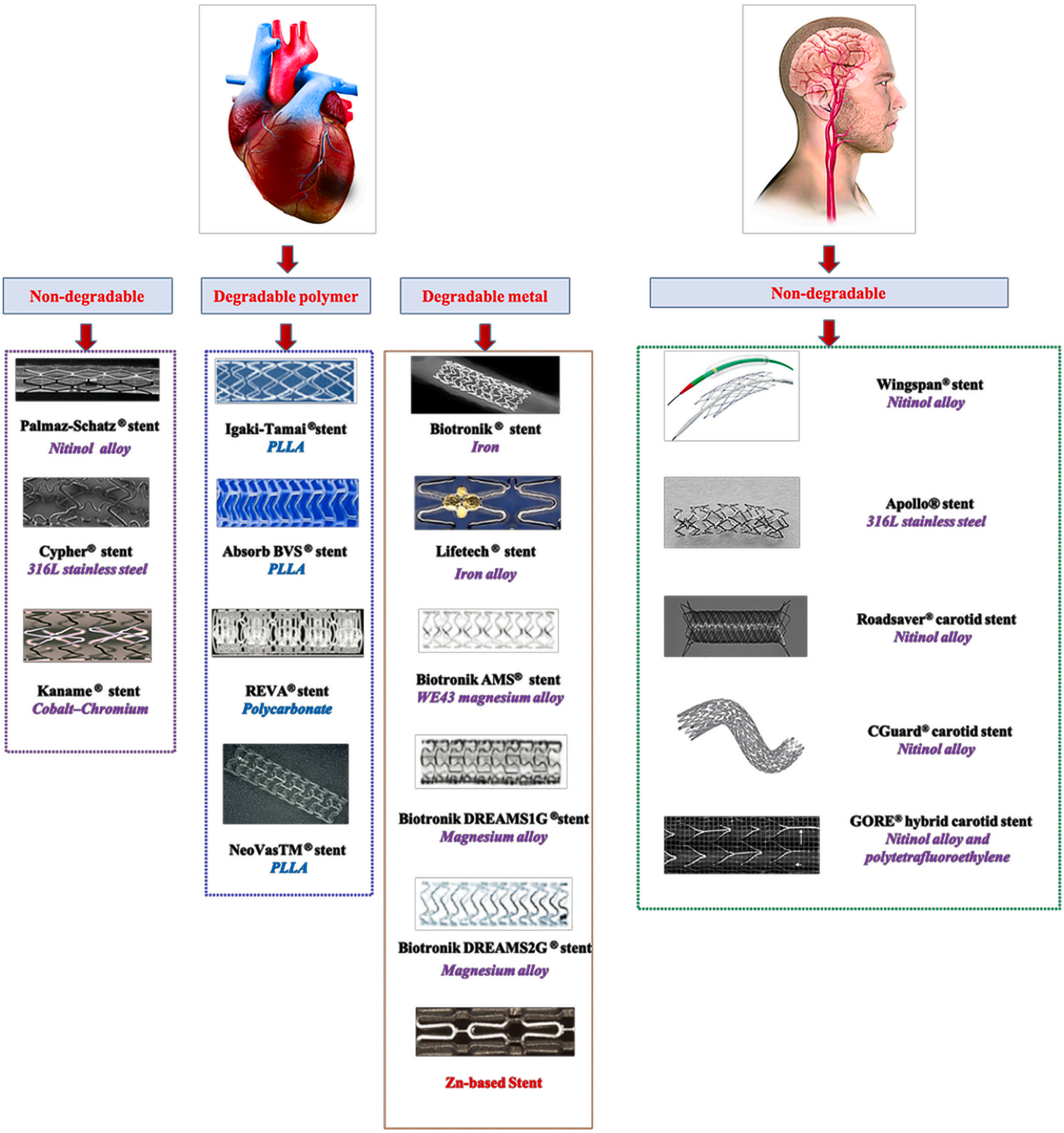

Fig. 10. The representative and commercially available stents for cardiovascular/cerebrovascular stenosis treatment [87–98]. The application of Zn-based stent is still in research [99].

4.2. Hemodynamics

It is well acknowledged that, due to the pulsatile nature of blood flow, the vessel cells are constantly subject to mechanical forces in the form of stretch, cyclic strain and shear stress [151]. Except for their effects on restenosis and thrombosis [152], the local hemodynamic forces after stenting also have a great influence on the corrosion behaviors of BMs. Mg alloys were more susceptible to corrosion in the flowing solution under shear stress [153,154]. Taking the carotid artery as an example, the cerebral blood flow rate varies greatly between a healthy person (400 ml/min) and an ischemic stroke patient (250 ml/min) [155]. In one study, Mg–Zn–Y-Nd alloys fabricated by sub-rapid solidification processing provide excellent corrosion resistance in dynamic SBF, which opened a new window for design of biomedical materials, especially for vascular stent application [156]. A research showed that the degradation behavior of BMs is different when tested under static and dynamic conditions [157]. Also, the amplitude of shear stress has a strong influence on the corrosion process, with higher shear stress resulting in faster corrosion rate of Mg alloys (Fig. 11) [152]. In addition, coating technology can be used to regulate the corrosion

Table 1
The *in vivo* studies of the Mg-based, Fe-based and Zn-based BM vascular stents.

BM stent	*In vivo* study		Mg Alloy	Fe Alloy	Zn Alloy	Reference
Cardiovascular	Animal	Rat	✓	✓	✓	Mg [109–112]: Fe [113]: Zn [114, 115]:
		Rabbit	✓	✓	✓	Mg [116–118]: Fe [63,64, 119–122]: Zn [74]:
		Porcine	✓	✓	✓	Mg [123–130]: Fe [62, 131]: Zn [3,132, 133]:
		Sheep	✓			Mg [134]:
	Clinical	Single-center				Mg [135]:
		Multi-center	✓			Mg [136–138]:
Cerebrovascular	Animal	Rat	✓			Mg [37,52]:
		Rabbit	✓			Mg [38,53, 139]:
		Porcine				
		Sheep				
	Clinical	Single-center				
		Multi-center				

behavior of the substrate in the fluid or blood environment, so that it can play a better temporary support role [158].

4.3. Neuro-cytocompatibility

Magnesium is an essential trace element in the human body [160]. Magnesium sulfate has been used as a promising neuroprotective agent, which has been verified in several animal and single-center studies of cerebral ischemia treatment [161]. Mg ion is involved in a series of physiological functions such as nucleic acid metabolism, signal transduction, gene expression, apoptosis regulation and endocrine regulation. For ischemic stroke patients, the occluded blood vessels can lead to ATP depletion, ischemic depolarization and abnormal calcium influx, which can cause neural cell necrosis or apoptosis [162]. Mg ion can inhibit the calcium influx and the excitatory amino acids release into neurons, reduce the calcium-induced mitochondrial dysfunction and preserve cellular energy metabolism. Besides, the potential neuroprotective function of magnesium can also be reflected in expanding vessels to promote blood circulation, inhibiting platelet aggregation and increasing red blood cell deformability [163]. In the case of Mg-based alloys, Mg^{2+} is mainly derived from their degradation products. In one study, bare Mg-Nd-Zn-Zr stent was implanted in rabbit CCA [164], and one month later, the outer part of the stent was *in situ* replaced by the degradation products, which mainly consisted of Ca, Mg, P and O. Unbehau et al. evaluated the influences of brain cell activity on magnesium degradation, including glioblastoma multiforme cells, microglia cells and primary astrocytes, and their study suggested that the degradation behavior of Mg was cell type/density-dependent [165]. The concentration of Mg ions in heart, brain and blood stayed relatively stable, showing no statistically significant difference to that of the negative control (Fig. 12).

4.4. Alloying elements selection

Due to the complexity of cerebrovascular vessels, it is necessary to select stent materials with higher elastic modulus and better elasticity. The biodegradable behaviors and mechanical properties of Mg alloys are tunable by suitable alloying elements [166]. Metals with low hydrogen overvoltage, including Ni, Fe, and Cu, can cause severe galvanic corrosion of magnesium alloys, while others like Al, Zn, Cd and Sn can induce a much lower corrosion rate [167]. The incorporation of Nd and Zn can improve the mechanical properties of Mg alloys through solid solution strengthening and precipitation strengthening techniques. Due to the small potential difference between the α -Mg matrix and the second phase $Mg_{12}Nd$, no severe local corrosion was observed *in vitro* [168]. Zr is a commonly used grain refiner in Mg alloys, which can improve mechanical properties and corrosion resistance [169]. A study reported that Mg–1Mn and Mg–1Zn alloys showed low current densities in both SBF and Hank solutions, which provided evidence that Mn and Zn could improve the corrosion resistance of Mg alloys [166].

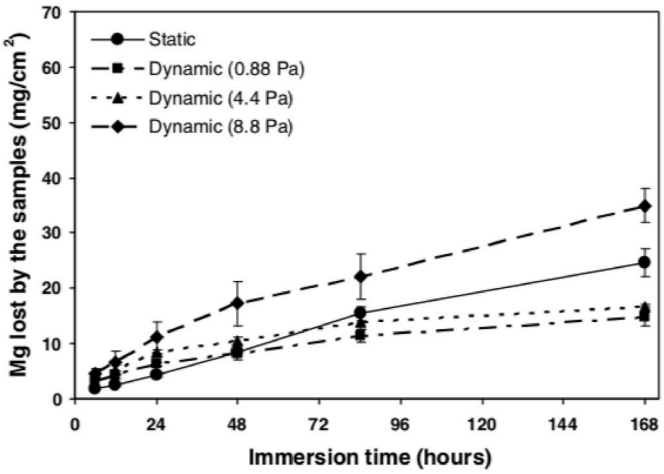

Fig. 11. Mean magnesium loss as a function of test duration. It was measured by atomic absorption spectrometer for 168 h at a shear stress of 0, 0.88 Pa, 4.4 Pa and 8.8 Pa with different hemodynamics conditions [159].

Table 2
Detailed information on degradable magnesium alloy stents.

Stents Pictures			
Name/Years	AMS-1/2007 [91]	DREAMS 1 G /2013 [91]	DREAMS 2 G /2016 [87]
Strut material	93% magnesium and 7% rare earth elements (WE43)		
Coating material	None	PLGA	PLLA
Eluting drug	None	Paclitaxel	Sirolimus
Degradation (Months)	4	9	9
Highlights in clinical results	● AMS stents can be safely degraded after 4 months of implantation [136].		
	● The failure rate of DREAMS 1 G stent was 3.6% at 3 years, without cardiac death or stent thrombosis [137].		
	● DREAMS 2 G stent were relatively safe and no clinical events occurred after 6–12 months implantation [138].		

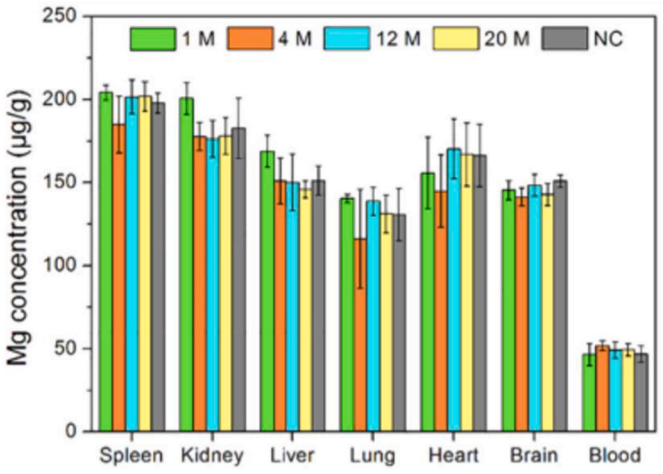

Fig. 12. The concentration of Mg in the spleen, liver, lung, kidney, heart, brain and blood of rabbits after 1 month (n = 3), 4 month (n = 3), 12 month (n = 2), 20 month (n = 2) implantation of BMs and NC (non-specific control) [53].

Table 3
The effects of some potential alloying elements on cerebrovascular disease.

Element	Normal concentration in blood or cerebrospinal fluid	Effects on cerebrovascular disease
Mg	2.74 ± 0.10 mg/dL [172]	✓ Having neuroprotective effects on stroke patients [162].
Ca	4.95 ± 0.70 mg/dL [172]	✓ Reducing blood pressure ✓ Reducing stroke incidence rate [173].
Zn	17.40 ± 9.50 μg/dL [172]	✓ Scavenging free radicals ✓ Reducing DNA damage ✓ Reducing Cognitive Impairment Following Traumatic Brain Injury [67].
Cu	15.70 ± 13.50 μg/dL [172]	✓ Making red blood cells ✓ Maintaining nerve cell activity [174].
Fe	13.10 ± 3.60 μg/dL [172]	✓ Playing an essential role in erythropoiesis, immunity, and oxidative metabolism [175].
Mn	2.50 ± 0.70 μg/dL [172]	✓ An essential dietary metal critical for healthy cellular function ✓ Having an impact on dopamine, glutamate, and GABA neurotransmission in the basal ganglia [176].
Ni	~5.5 mg/L [177,178]	✓ Affecting specifically voltage-dependent calcium channel (VDCC) types, ligand-gated channel, and the NMDA receptor (NR) channel ✓ Exacerbating neuronal injury by potentiating the activity of NR2B-containing NRs in developing neurons [179,180].
Al	4–10 μg/L [181]	✓ Influencing the processes of apoptosis and necrosis ✓ Potentiating the inflammatory events leading to tissue damage for the management of ischemic brain injury ✓ Binding to various metal-binding proteins and influencing homeostasis of other metals [182,183].
Se	–	✓ Being involved in antioxidant defense ✓ Keeping the maintenance of intracellular redox balance [184].

The influences of the added elements on the metabolic process should also be considered [170]. The normal concentration of Mg in the blood is around 14,130 ± 649.2 μmol/L [171]. As listed in Table 3, some trace elements may have positive effects on cerebrovascular diseases and maintain the healthy state of cerebral blood vessels.

In addition to the biocompatibility of element X in the nervous system, Mg-X alloying and the effects of X on the mechanical properties, corrosion properties, blood compatibility and nerve cells of alloys should also be considered. At the same time, it is necessary to explore whether the corrosion products and dissolved ions can still play the nerve function.

5. Conclusion and future work

With the development of material science, BMs have been fabricated into biodegradable medical devices to circumvent potential side effects from permanent implants. The application of BMs in neuroscience is still in its infancy. Compared with Fe-based and Zn-based alloys, as well as Molybdenum and Tungsten, Mg-based alloys show good neurocytocompatibility and have proper and tunable corrosion rate and mechanical properties. Several pioneering works have been conducted on Mg alloys for their application in neuroscience, such as filament within nerve conduits to accelerate nerve regeneration, nerve electrode for neural recording, and stents for carotid artery stenosis and aneurysm treatment. Besides, Mg ions can be used as neuroprotective agent. Based on the novel research and inspired by the promising clinical results from cardiovascular Mg alloy stents, we propose that Mg alloys could be highly promising BMs to make cerebral vascular stent for ischemic stroke treatment. Future work should be done to design novel Mg-based alloys and optimize the stent geometry to ensure their biomechanical compatibility with brain blood vessels and a mild and safe *in vivo* degradation.

Declaration of competing interest

We declare that we have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

This work was supported by the National Natural Science Foundation of China (82027802, 82102220, 82071468), Beijing Municipal Natural Science Foundation (721220, 61975017) and General Projects of Scientific and Technological Plan of Beijing Municipal Education Commission (KM202010025023).

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