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Intracerebral hemorrhage in mouse models: therapeutic interventions and functional recovery

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Abstract

There has been strong pre-clinical research on mechanisms of initial cell death and tissue injury in intracerebral hemorrhage (ICH). This data has led to the evaluation of several therapeutics for neuroprotection or the mitigation of early tissue damage. Most of these studies have been done in the rat. Also, there has been little study of the mechanisms of tissue repair and recovery. This review examines the testing of candidate therapeutics in mouse models of ICH for their effect on tissue protection and repair. This review will help the readers compare it to the extensively researched rat model of ICH and thus enhance work that are pending in mouse model.

Keywords

ICH; Collagenase; Autologous blood; Functional recovery

Introduction

Focal stroke is one of the leading causes of death and chronic disability in the United States (Centers for Disease and Prevention 2009; Minino et al. 2011; Go et al. 2013b) and can be broadly classified into ischemic stroke and intracerebral hemorrhage. Ischemic stroke, due to its vast occurrence, has been extensively studied and reported. In the past decade more researchers have started to delve into hemorrhagic stroke, the second common stroke subtype, accounting for 13–15 % of all stroke cases in the United States (Go et al. 2013b). Overall spontaneous brain hemorrhage, based on its location, can be categorized into intracerebral, sub-arachnoid, epidural and subdural (Caplan 2009). Here, we focus only on the intracerebral hemorrhage as it is a subtype of focal stroke and the most common form of brain hemorrhage (Go et al. 2013a).

Intracerebral hemorrhage (ICH) occurs due to a breach of a cerebral vessel causing leakage of blood inside the brain parenchyma. Uncontrolled hypertension is a major modifiable risk factor and the leading cause of ICH (Centers for Disease and Prevention 2013; Gillespie et al. 2013; Badjatia and Rosand 2005) with age increasing the incidence progressively

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(Ariesen et al. 2003; Aguilar and Freeman 2010; Broderick et al. 1999). One other condition with increased ICH incidence in population aged 60 and above is cerebral amyloid angiopathy (CAA), where cerebral blood vessels are deposited with amyloid proteins (Pontes-Neto et al. 2012; Tang et al. 2013). CAA-induced hemorrhages are usually widely distributed in the brain and recurrent in nature (Tang et al. 2013). The bleeding events in amyloid angiopathy also involve microbleeds and an association with amyloid vascular and neuropathology, placing this disease as distinct from other forms of spontaneous ICH and requiring separate modeling systems that are outside the scope of this review (Dierksen et al. 2010).

Despite strong preclinical research on ICH, the treatment still remains the same, with poor prognosis. ICH is devastating due to its high fatality rate, with 30-day fatality reaching up to 50 %, and very high morbidity rate with only 1 in 5 who survive the hemorrhage progressing to functional independence at 6 months (Counsell et al. 1995; Broderick et al. 2007; Adeoye and Broderick 2010). Pre-clinical models of ICH are critical to study the mechanisms of this severe mortality and morbidity and to understand possible process of repair and recovery. The goal here is to review the potential therapeutic targets that are currently tested in a mouse model of ICH that shows promising evidence for functional recovery.

Modelling ICH

Several animal models capture elements of human ICH to an extent, with each model having its own pros and cons (Krafft et al. 2012; Leonardo et al. 2012). Here we mention the two most commonly used models 1. Collagenase model: where injection of a bacterial enzyme digests the collagen present in the basal lamina of the blood vessels to produce spontaneous brain hemorrhage (Rosenberg et al. 1990; MacLellan et al. 2002; Chesney et al. 1995; MacLellan and Colbourne 2005; Wu et al. 2011). 2. Blood infusion model: where a fixed amount of blood (autologous or donor) is injected in to the brain parenchyma to mimic a primary accumulation as in human ICH (Bullock et al. 1984; Belayev et al. 2003; Nakamura et al. 2004; Rynkowski et al. 2008). The collage-nase model is comparatively well studied due to its ease of approach and the fact that the source of the hemorrhage is a spontaneous vascular leak. However, this model has the drawback of disrupting a larger brain area due to multi-vessel damage and inducing a severe inflammatory response that might cause neuronal toxicity to adjacent areas (Leonardo et al. 2012). Much of the animal modeling in ICH has been done in the rat. However, the mouse has had increasing utility in ICH modeling because of the possible use of transgenics for molecular studies, the smaller brain size for drug distribution in direct infusion studies and the ability to utilize advanced in vivo imaging approaches, such as optogenetics.

Mechanisms of ICH-related brain damage

It becomes imperative to know the progression of brain damage before any therapeutic targets can be used as a treatment for ICH. There are several mechanisms that contribute to the brain damage that leads to neurologic deficit. The primary damage is due to the mass effect of hematoma formation and its increasing pressure on adjacent structures that displaces nearby white matter and blood vessels. Secondary damage results from several mechanisms including collection of blood breakdown products (iron, heme, etc.), activation

of thrombin, and an inflammatory- and immunogenic response of the brain due to hemorrhage (Xi et al. 2006). The mechanisms of ICH-related damage are reviewed in detail elsewhere (Xi et al. 2006; Keep et al. 2012). A schematic illustration of ICH-related brain damage and the potential therapeutic targets tested in a mouse model are shown in (Fig. 1). Though ICH is modelled most commonly by either collagenase- or blood-infusion, the differences in the mechanisms and the progression of damage are not well studied. MacLellan and colleagues tested the differences between these 2 models in rat by matching the hematoma volumes. They showed the collagenase model had a progressively expanding hematoma with greater tissue damage and lasting neurologic deficit in comparison with the blood model, where they showed lesser tissue damage and complete recovery from neurologic deficits (MacLellan et al. 2008). More research needs to be done in establishing the mechanisms of damage in both models to have better therapeutic targets.

Potential targets for ICH treatment

There is an increasing use of mouse models of stroke due to their advantages in transgenic and gene modification approaches. However, there is less systematic development of mouse models of intracerebral hemorrhage. Here, we review the different therapeutic approaches that have been applied to mouse models of ICH, including pharmacologic, gene and stem-cell studies. Among the two main types of hemorrhage, the collagenase model is most studied. Additional work needs to be done on the blood-induced ICH model for better understanding of ICH.

Pharmacologic targets that block proinflammatory mediators

Therapeutic approaches in animal models target several elements in the early cascades of tissue destruction in ICH, either to suppress or remove them and allow the damaged brain tissue to recover from progressive insult, or to promote active functional recovery. With direct blood extravasation into brain, secondary inflammation is a substantial feature. Drugs which reduce neuroinflammation enhance functional recovery. Lei and colleagues targeted tumor necrosis factor alpha (TNF-α), a cytokine that is secreted by the microglia in response to injury and acts as a prime neuroinflammatory mediator causing progressive damage. A single dose of TNF-α antibody, CNTO5048, via tail vein 30 min following collagenase-induced ICH in mice showed evidence of reduced neuroinflammation and improved functional deficit in the rotorod task (Lei et al. 2013). Similarly, TNF-α antagonist, R-7050 is tested with collagenase-induced ICH mice. Single dose of Intraperitoneal R-7050 given within 2 h of ICH showed reduced edema and blood brain barrier damage with improved neurological deficit assessed from modified 24 point scale (King et al. 2013).

Toll-like receptors (TLRs) are transmembrane proteins that recognize a variety of molecules or ligands that are associated with pathogens to elicit the innate immune response. TLRs acts predominantly via two signaling pathways 1. Myeloid differentiation primary response gene 88 (MyD88) signaling that activates nuclear factor kappa B (NFκB), a transcription factor involved in regulating proinflammatory cytokines. 2. Toll/IR-1 domain containing adaptor protein inducing interferon-beta (TRIF) signaling that expresses interferon, both contributing to the inflammatory response. Among several TLRs, TLR-4 is well studied and predominantly present in the microglia (Fang et al. 2013). In a recent study, TLR-4 was

blocked in a mice model of blood-induced ICH using the antagonist TAK-242. The treatment was given at 3 mg/kg IP once daily for 5 days with first dose given 6 h after ICH. The treated mice showed decreased inflammatory changes and brain edema with down regulation of several downstream inflammatory mediators. In addition, the treated mice also showed an improved neurological deficit based on a 28-point neurological scale testing, suggesting functional recovery (Wang et al. 2013). Similarly, TT-301 is a microglial inhibitor that blocks proinflammatory cytokines in response to brain injury. Collagenase-induced ICH mice treated with TT-301 at 1 mg/kg IP, first dose at 30 min and second dose at 6 h after ICH, and continued twice daily for 5 days, showed reduced cerebral edema. In addition, the treated mice showed improved performance in rotorod task (James et al. 2010). A schematic illustration of potential targets tested in mouse models of ICH is shown in Fig. 1.

Pharmacologic targets that block immune response

ICH causes robust myeloid (infiltration of monocytes and neutrophils and activation of microglia/macrophage) and lym-phoid (T-cell) immune responses. Both induce several inflammatory mediators near the injury site causing edema, cell death and functional deficits. Though several studies targeted a reduction in neuroinflammation in general, some studies specifically target T-cell induced immune response. FTY720 (Fingolimod), a sphingosine-1-phosphate (S1P) analog that acts on S1P receptors present on T-cell to down-regulate it and thereby causing lymphopenia and T-cell immune-suppression. FTY720 1 h following collagenase-induced ICH showed evidence of decreased edema at the injury site and improved performance on beam balance, wire hang task and an improved modified Garcia score. This score assesses spontaneous activity, side stroke, vibrissae touch, limb symmetry, lateral turning, forelimb walking and climbing (Rolland et al. 2011). Similarly, Fingolimod decreased lymphocytic infiltration and lowered sensorimotor deficits in both collagenase- and blood-induced ICH mice models (Rolland et al. 2013).

Neuroprotectants

The injured brain responds quickly with several endogenous neuroprotectants to limit the progressing brain damage. Several mechanisms including anti-inflammatory (covered above), anti-excitatory, anti-oxidative, neurotropism may contribute neuroprotective effects. One such neuroprotectant is apolipoprotein E (apoE), which may function as an immune modulating agent. It is limited because of inability to cross the blood brain barrier (Laskowitz et al. 2007). An ApoE mimetic peptide, COG1410, was able to overcome this limitation and was tested in a mouse model of collagenase-induced ICH. Mice treated with intravenous (IV) COG1410 at 2 mg/kg first dose within 2 h after ICH and subsequently every day/5 days showed several findings that reflect reduced neuroinflammation, which includes decreased microglial activation, cytokine interleukin (IL)-6 production and edema in comparison with saline controls (Laskowitz et al. 2012).

Retinoic acid (RA) is a well-established signaling molecule that plays a crucial role in neural development and differentiation and acts via a nuclear RA receptor (RAR) complex (Maden 2007). Its role in neuroprotection is mainly due to its anti-inflammation (Mey 2001, 2006) and up regulation of brain-derived Neurotrophic factor (Katsuki et al. 2009; Kurauchi et al.

2011). A recent study studied its effect on microglial activation, an important feature seen in neuroinflammation. Lipopolysaccharide caused microglia activation that showed increased RA catabolism along with increased nitric oxide, TNF alpha and cytochromes that are proinflammatory. Supplementation of RA attenuated microglial activation and lowered inflammatory mediators, indicating its role in anti-inflammation (Hellmann-Regen et al. 2013). Due to its neuroprotective effect and its specific role as a suppressor of microglial activation, RAR agonists such as Am80 and all-trans retinoic acid (ATRA) were tested in mouse model of ICH. Both treatments showed several neuroprotective features including reduction in the hematomal neuronal loss, decrease in the number of activated microglia/macrophages in the perihematomal regions and improved sensorimotor performance on beam-walking, rotorod and modified limb placement tests (Matsushita et al. 2011, 2012).

Minocycline, a semi-synthetic tetracycline derivative, is a neuroprotectant with anti-inflammatory, anti-oxidative, anti-apoptotic properties and a role in matrix metalloproteinase (MMP) inhibition (Stirling et al. 2005). It has been extensively tested in stroke models and moved into clinical trials (Kohler et al. 2013). Blood-induced ICH mice, when treated with two dose of minocycline, one at the time of ICH (either IP or intracerebral (IC) or both) and another 12 h (only IP) after ICH, showed reduced neuronal death, microglial activation and tissue loss. The maximum protective effect is seen with combined administration of minocycline by both intracerebral and Intraperitoneal route. Additionally, the treated mice showed improved performance in a grid walk and increased locomotion in open field maze (Xue et al. 2010). Similarly, Curcumin, a chemical derived from plant Curcuma longa Linn, has shown several neuroprotective properties including anti-oxidative (Thiyagarajan and Sharma 2004), anti-apoptotic (Zhao et al. 2010), anti-inflammatory (Aggarwal and Harikumar 2009) with detailed mechanisms reviewed elsewhere (Cole et al. 2007). ICH mice treated with curcumin 150 mg/kg IP, 15 min post ICH showed reduced brain edema, tissue loss and MMP + ve cells with improved deficit on grid walk and neurological score (Sun et al. 2011).

Other agents target anti-inflammatory, anti-oxidative and neuroprotective mechanisms in ICH. The neuroprotective and anti-inflammatory properties of nicotine are mediated in part via its nicotinic acetylcholine receptors (nAChRs)-α7 present in microglia/macrophages. Nicotine modulates TNF release to reduce microglial activation (Shytle et al. 2004; Suzuki et al. 2006). Collagenase induced ICH mice treated with daily administration of nicotine at 2 mg/kg IP, with first dose 3 h after ICH showed reduced activation of microglia/macrophages in the perihematomal areas and increased Striatal neuron survival associated with an increased expression of the antiapoptotic protein B cell lymphoma-2. In addition, the nicotine treated mice showed improved sensorimotor performance assessed on beam-walking, modified limb-placing and adhesive removal test with improved overall survival rate (Hijioka et al. 2011). Similar effects are seen with ICH mice treated with a direct α7 nAChR agonist (Hijioka et al. 2012).

Brain natriuretic peptide (BNP), an established marker of cardiac dysfunction, is also elevated during the acute phase of brain injuries. It has been proposed that this may relate to an endogenous anti-inflammatory role. James and colleagues tested Neseritide, a synthetic peptide similar to endogenous BNP, in collagenase-induced ICH mice. Neseritide at 8 μg/kg

IV, first dose at 30 min and second dose at 4 h after ICH, showed overall reduced neuroinflammatory response with decreased neural damage. The treated mice showed improved performance in rotorod and improved long term spatial memory on Morris water maze task (James et al. 2010).

Statins, though known mainly for their cholesterol lowering effect by inhibiting 3-hydroxy-3-methyl-glutaryl-coen-zyme A (HMG CoA) reductase enzyme, have several other beneficial effects as well. Their neuroprotective effects following ICH were extensively studied in rats (Jung et al. 2004; Seyfried et al. 2004; Karki et al. 2009; Ewen et al. 2013) but not in mice. A recent study by Laskowitz and colleagues tested the effects of statins on mouse model of collagenase-induced ICH. Mice injected with simvastatin at 1 mg/kg first dose within 1 h after ICH and subsequently every day/5 days showed improved vestibulomotor performance in rotorod task with improved overall survival rate (Indraswari et al. 2012). This suggests statins might act as a potential therapeutic following ICH and more research on molecular mechanisms will reveal its role in functional recovery.

Pharmacologic targets that block blood-induced toxicity

Apart from the neuroinflammatory damages in the brain due to hematoma, iron-induced toxicity causes significant damage. ICH of course causes a collection of blood components including red blood cells, thrombin, coagulation factors and complement components all contributing to the cytotoxic damage surrounding the hematoma. Red blood cell lysis releases hemoglobin, which degrades to hemin and is later phagocytized by macrophages to produce the toxic byproducts biliverdin, carbon monoxide and iron (Fang et al. 2013). These toxic products if not cleared cause progressive damage to the perihematomal areas and worsen the inflammatory changes. Deferoxamine (DFX) is an iron chelator that has been extensively studied in rats (Nakamura et al. 2003; Wan et al. 2006; Okauchi et al. 2010; Hatakeyama et al. 2011, 2013). Wu and colleagues tested DFX in a mice model of collagenase-induced ICH. DFX was given at 200 mg/kg IP, first dose 6 h after ICH, and subsequently every 12 h for 3 days. The treated mice showed reduced damage with reduced inflammation, neuronal death, iron accumulation and reactive oxygen species in the region of insult. In addition, the treated mice showed evidence for an improved neural deficit score (Wu et al. 2011).

Another method to remove the blood-induced toxicity is to actively enhance the hematoma clearance thereby reducing inflammation and damage. Peroxisome proliferator-activated receptor-γ (PPAR-γ) is a transcription factor that activates expression of several enzymes responsible for reducing oxidative stress associated with the hematoma and promotes CD-36 mediated phagocytosis to clear toxic byproducts from blood. In addition, it inhibits NFκB-induced inflammatory cytokine response (Aronowski and Zhao 2011). A PPAR-γ agonist, Rosiglitazone, has been used to test the mass effect of the hematoma and its resolution in a mouse model of blood-induced ICH. The treatment enhanced PPAR-γ regulated gene expression and hematoma resolution, with a decrease in proinflammatory gene and neuronal damage (Zhao et al. 2007). A list of pharmacologic manipulations tested in a mouse model of ICH is shown in Table 1

Stem-cell based approach

Pharmacologic approaches target one or a limited number of molecular pathways over a short treatment window whereas stem-cell based therapies aim is to replace damaged cells and induce local repair in the perihematomal brain for longer duration. Lee and colleagues tested the effect of immortalized human neural stem cells (hNSCs) in a mouse model of ICH. One week after ICH, they used hNSCs obtained from primary human fetal Telencephalon (neural progenitor cells) for intracerebral transplantation. The transplanted mice showed better cell survival, migration and differentiation into neurons and glial cells with improved performance and functional recovery assessed by rotorod and modified limb placement task (MLPT) (Lee et al. 2007a). Though transplantation of neural stem cells in the injured brain area shows promising results, it is still in an early phase before clinical trials due to the low survival rate of transplanted cells in animal studies. The injured brain may create an environment that is unfavorable for the NSCs survival. To improve this, therapies are targeted to improve neural stem cell survival by overexpressing growth factors and molecules that favor cell survival and neuroprotective. Several studies have indicated that transplantation of neural stem or progenitor cells that overexpress growth factors or signaling molecules such as vascular endothelial growth factor (VEGF), glial cell line-derived growth factor (GDNF), brain-derived Neurotrophic factor (BDNF) or AKT1 after ICH show improved functional recovery in the treated mouse (Lee et al. 2007b, 2009a, b, 2010). These studies show targeted increased expression of specific signaling molecules or factors locally near the transplanted area with improved survival of transplanted cells. These studies however have serious limitations of unregulated continuous expression of signaling molecules that might ultimately be detrimental over a long course. Future work needs to be done on a controllable or inducible expression system for a gene that is introduced into a stem/progenitor cell for transplant. A recent study tested the combination of fibroblasts plus gene therapy by transplanting BDNF-transfected 3 T3 fibroblast cells in a mouse model of ICH. The treatment increased BDNF expression, recruited migratory neuroblasts and increased reactive astrocytes in the perihematomal areas with evidence of improved functional recovery (Chen et al. 2012b). A list of gene and cell based manipulation tested in a mouse model of ICH is shown in Table 2

Transgenic mouse studies

An advantage of studying the molecular mechanisms of hemorrhagic stroke in a mouse model is to selectively target the signaling molecules using a transgenic approach. For example matrix metalloproteinases (MMPs) are proteolytic enzymes that are involved in blood brain barrier disruption and damage during ICH. Selective removal of MMPs should lower brain damage and enhance recovery. This was tested with collagenase-induced ICH in MMP-12 deficient mice that showed decreased microglia/macrophage activation evidence for anti-inflammatory changes with improved sensorimotor function (Wells et al. 2005). Similarly and as described earlier, Toll like receptors (TLRs) proteins play a crucial role in neuroinflammatory damage following stroke. Autologous blood-induced ICH in TLR-4 deficient mice showed reduced inflammatory changes in the perihematomal areas with improved performance on a forelimb motor control task (the cylinder task) and showed increased mobility in an open field maze (Sansing et al. 2011). Both pharmacologic and

transgenic approaches of TLR manipulation show strong evidence for its inflammatory role in ICH, and blocking TLR shows robust improvement in both cellular and functional measures. Similarly, collagenase-induced ICH to Chemokine knockout mice (CCL2–/– and CCR2–/–) showed reduced hematoma volume and neuronal loss with decreased infiltration of neutrophil and leucocyte. Additionally, they showed persistent neurological deficit over time with reduced recovery. These mice when infused with CCL2 showed better recovery and findings similar to wild type mice. In addition, they showed improved neurological deficit in NDS (Yao and Tsirka 2012). Future studies will likely aim to apply greater transgenic or selective gene alteration approaches to precisely study the involvement of signaling molecules involved in ICH.

Alteration of temperature

Here we discuss ICH studies that altered temperature to show its beneficial effect on functional recovery. Therapeutic hypothermia (TH) is defined as a controlled decrease in the body temperature and can be classified into mild (34–35.9 °C), moderate (32–33.9 °C), moderate/deep (30–31.9 °C) and deep (<30 °C) (Polderman and Herold 2009; Groysman et al. 2011). Most pre-clinical studies use mild to moderate TH as a target temperature to study the beneficial effects. Similarly, hyperthermia can be classified into mild (37.5–38 °C), moderate (38.1– 38.5 °C), moderate/severe (38.6–38.9 °C) and severe (≥39 °C) (Polderman and Herold 2009). Both hypo-and hyperthermia are tested following hemorrhagic stroke to reveal whether altering the body temperature has a role on functional recovery.

Therapeutic hypothermia (TH) is a well-studied medical treatment, which has shown several beneficial effects following ischemic (non-hemorrhagic) stroke (Wu and Grotta 2013; Klassman 2011), but less is known about the role of TH in hemorrhagic stroke, particularly in a mouse model. ICH studies from rat literature using TH demonstrate mixed results on functional recovery, with some works demonstrating beneficial (MacLellan et al. 2004, 2006; Fingas et al. 2009) and others showing no or deteriorating effects (MacLellan et al. 2002; Fingas et al. 2007). This mixed effect might result from several sources, including selection of stroke models (collagenase vs. blood), time the treatment was induced after ICH, duration of the treatment, methods to induce hypothermia, etc. which are reviewed elsewhere (MacLellan et al. 2009).

Pharmacologically induced hypothermia (PIH) is a more efficient way to induce HT that uses pharmacological agents to lower the set point in the brain thermoregulatory center. This method avoids activation of compensatory thermoregulatory mechanism thus preventing discomforts due to physical cooling methods. Neurotensin (NT), is one such agent, but normally unstable and does not cross the blood brain barrier to act on its NT receptors (NTR) whereas, HP1–201, NTR agonist, is a more stable compound that can penetrate into the brain to act on the NTR1 receptor. A recent study used this hypothermic agent in a mouse model of ICH to test its effect on functional recovery (Wei et al. 2013). This study demonstrated, a single dose of HP-201, when given 1 h post-ICH, reached hypothermia in 30 min and lasted for approximately 6 h resulting in several neuroprotective changes with mice showing significant evidence for functional recovery. The protective effects lasted even when the treatment was given 24 h post-ICH with trend showing functional recovery.

This shows PIH should be introduced before 24 h following ICH to be neuroprotective and thereby enhance functional recovery.

Though lowering the body temperature alone showed some evidence for recovery, combined therapy may provide additional benefits. TH was combined with rehabilitative therapy and with Xenon in the two studies that sought to evaluate such a combined approach. Xenon (Xe) is a neuroprotectant, mainly due to its antiexcitotoxic effect, by inhibiting activation of N-methyl-D –aspartate (NMDA) receptors and its downstream targets, along with its anti-inflammatory and anti-apoptotic properties (Deng et al. 2014). Due to its several neuroprotective mechanisms, it was hypothesized that Xe would add benefit to TH. Rats with temporary focal ischemia, when treated with 30 % Xenon combined with hypothermia (36 °C) for 20 h, showed improved neurological score and reduced infarct volume at 4 weeks, but no beneficial effect when the same treatment was combined at normal temperature 37.5 °C (Sheng et al. 2012).

Rehabilitative therapies have also been added to TH. In a strict sense this addition of TH plus a behavioral treatment does not represent “combination therapy” in the way that two neuroprotective agents are combined. Instead, this represents a closer modeling of real-world conditions for ICH patients. For example, Colbourne group tested this combination of hypothermia and constrained-induced movement therapy (CIMT) in a collagenase-induced ICH rats. Hypothermia (33 °C for 24 h and then 35 °C for another 24 h) and rehabilitation (CIMT for 7 days) were given 12 h and 2 weeks post-ICH, respectively. Combined therapy showed improved recovery on a stair-case test of forelimb use, whereas CIMT therapy alone produced significant improvement similar to combined therapy on a limb use asymmetry test (MacLellan and Colbourne 2005). Though combined therapies have shown some beneficial effects in certain tasks, further research needs to be done to show the consistent effects of this approach in different stroke models.

Based on the beneficial effects of hypothermia one would predict that ICH would worsen in hyperthermia. MacLellan and Colbourne tested this in a rat model of collagenase-induced ICH and demonstrated that hyperthermia (>38.5 °C) did not worsen the injury nor the functional outcome in spontaneous forelimb use and skilled reaching tasks (MacLellan and Colbourne 2005). Similarly, hyperthermia (39 °C for 3 h) when tested on a rat model of blood-induced ICH showed no evidence of deteriorating effects on functional recovery. Rather it showed some improved behavioral outcome assessed by a neurological deficit score (Penner et al. 2011). This unexpected effect of hyperthermia without any deteriorating effects on both hemorrhagic stroke models needs further investigation to understand its validity across models and species. Though the effects of altered temperature on functional recovery varied in rats, currently, it is not known, whether similar effects will be seen in a mouse model.

Rehabilitative approaches

In pre-clinical ICH models post-stroke rehabilitation is an effective way to lower the neurological deficit and enhance functional recovery. Work in rat ICH has shown promising beneficial effect of exercise on functional recovery (MacLellan et al. 2011; Tamakoshi et al. 2014; Takamatsu et al. 2010), but less is known in mouse models. Jin and colleagues tested

exercise in a mouse model of collagenase-induced ICH and found that mice that received voluntary exercise showed increased proliferation and survival of neural progenitor cells (NPCs), with migration of cells to the injured site in comparison with no exercise mice. These findings relate to cellular mechanisms (neurogenesis) that are commonly associated with neural repair and recovery following stroke damage, but this study did not measure functional recovery (Jin et al. 2010). A recent study showed collagenase-induced mouse ICH caused increased neurogenesis on day 7 in perihematomal areas and activation of NGF-TrkA and BDNF-TrkB signaling cascade, suggestive of an involvement of these cascades in brain repair following ICH. Mice that received exercise 4 days after ICH for 10 days (Treadmill) showed enhanced BDNF signal and TrkB receptor activation. This result suggests an active role of this signaling cascade and its regulation by exercise that might be involved during recovery (Chen et al. 2012a). More work need to be done to identify other signaling pathways exclusively involved during rehabilitative treatments.

The inability to translate a strong preclinical stroke research into successful clinical treatment leads to recommendations by Stroke Therapy Academic Industry Roundtable (STAIR) to enhance the quality of animal research (Fisher et al. 2009). STAIR recommends a list of measures to be followed during preclinical research. In this review we examined whether the studies listed in the tables report on measures of randomization, blinded assessment of outcome and sample size calculation. Of the 23 studies examined all reported blinded assessment of outcome, 56 % reported on randomization and no study reported sample size calculation. This suggests more reporting on certain measures are needed as recommended by STAIR to improve the quality of preclinical research.

Conclusion

Preclinical research has contributed significantly to our understanding of cellular and molecular mechanisms of ICH. Mouse models of ICH are growing in use for their ability to provide genetic manipulation in discovery science and for their overall ease of use in experimental surgery and manipulation. In ICH, several potential therapeutics that target neuroprotection and neural repair were tested successfully to show functional recovery. Yet, the results have been hard to translate into clinical studies. This might be due to inability in replicating human ICH in the current animal models. New techniques should evolve to overcome this situation. Currently, the collagenase model of ICH is more prevalent and less is known on blood-induced ICH. Selective molecular targets that are involved in neural repair and recovery using transgenic approaches are lacking and further work is needed. Preclinical studies should combine therapeutics with rehabilitation for an approach that more closely resembles the clinical situation and approach that might yield a better translation into clinical medicine.

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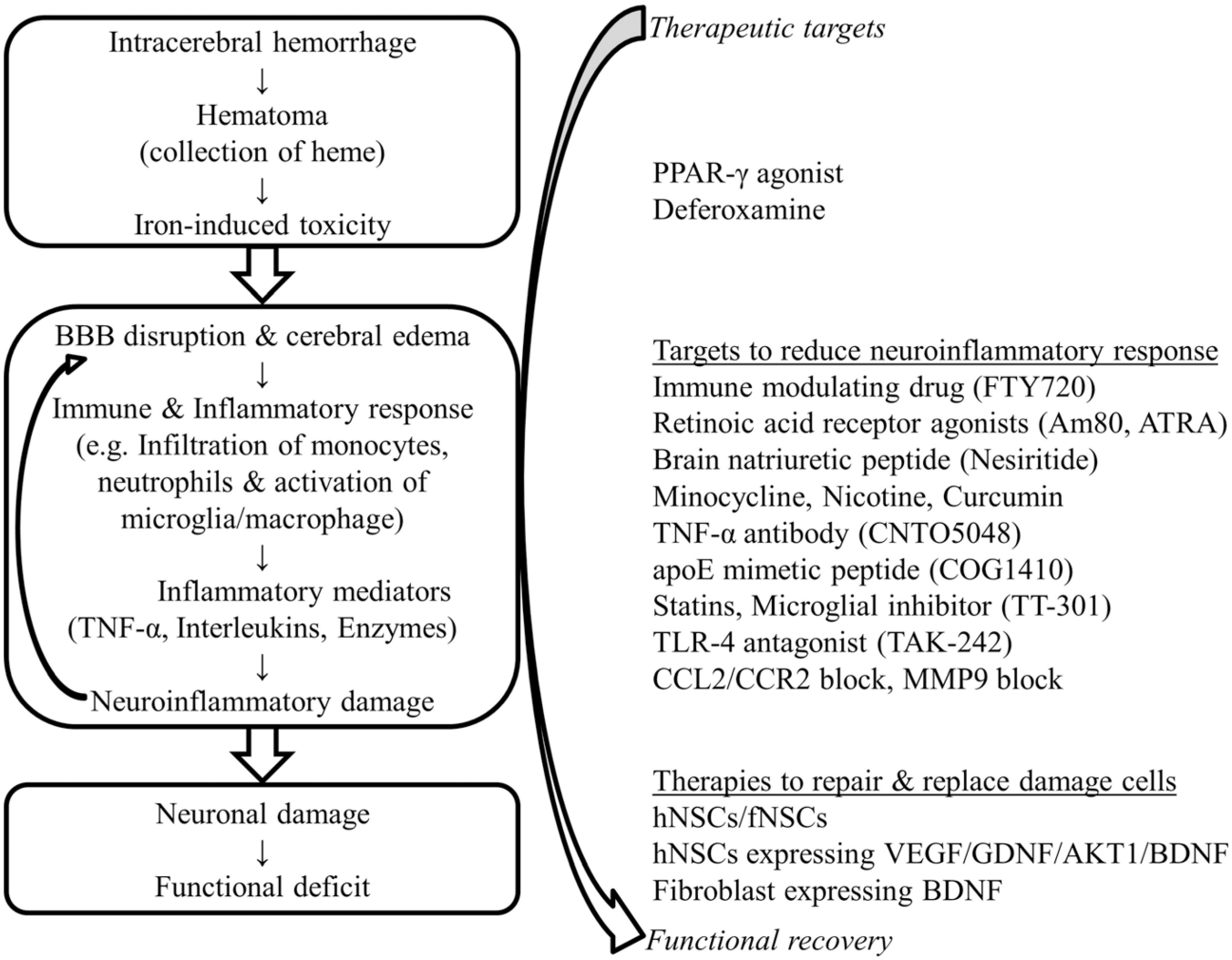

Fig. 1.
Illustration of potential targets acting at different phases of ICH

Table 1

List of pharmacologic targets tested in a mouse model of ICH

Drug/Peptide/Chemical	Behavior	Other Major Effects	References
Collagenase-induced ICH			
TNF-α antibody CNTO5048	Improved vestibulomotor function (VMF) assessed by Rota-rod (RR) test	↓ neuroinflammation	Lei et al. (2013)
apoE mimetic peptide (COG1410)	Improved VMF (RR test), composite neuro severity scores & ↓ mortality	↓ neuroinflammation, cerebral edema	Laskowitz et al. (2012)
Microglial inhibitor TT-301	Improved VMF (RR test)	↓ cerebral edema	James et al. (2012)
Simvastatin	Improved performance (RR test)	↑ survival rate	Indraswari et al. (2012)
Retinoic acid receptor agonist (ATRA & Am80)	Improved sensorimotor performance (SMP) assessed by beam-walking (BW) and modified limb-placing test (MLPT)	↓ # of activated microglia/macrophages, damage of axon tracts & neuron loss	Matsushita et al. (2012)
Nicotine	Improved SMP assessed by BW, MLPT & adhesive removal test (ART), ↑ survival rate	↑ expression of anti- Vs. pro-apoptotic protein ↓ activation of microglia/ macrophages, neutrophil infiltration, oxidative stress & apoptosis	Hijioka et al. (2011)
Immune-modulating drug FTY720	Improved composite neurological deficit score (NDS) assessed from modified Garcia test, ↑ scores in modified beam balance & wire-hanging tests	↓ brain edema	Rolland et al. (2011)
Iron chelator Deferoxamine	Improved composite NDS assessed from body symmetry, forelimb symmetry, gait, climbing, circling, compulsory circling but no improvement on individual tests	↓ neuronal death, perihematomal iron accumulation, microglial activation, neutrophil infiltration & ROS	Wu et al. (2011)
Retinoic receptor agonist (AM80)	Improved SMP assessed by BW, RR test & MLPT	↓ # of loss of Striatal neurons, # of activated microglia/macrophages, & oxidative stress in perihematomal regions	Matsushita et al. (2011)
Brain Natriuretic peptide (Neseritide)	Improved VMF (RR test) & long-term spatial memory (Morris Water Maze) performance	↑ cerebral blood flow ↓ activated microglia, neuronal degeneration & neuroinflammatory markers	James et al. (2010)
Blood-induced ICH			
Toll-like receptor antagonist (TAK-242)	Improved composite NDS assessed using 28-point neurological deficit scale. Individual tests not reported.	↓ brain edema, inflammatory factors (TNF-α, IL-1β, IL-6), DNA damage, perihematomal neuronal degeneration & expression of signaling molecules downstream of TLR-4	Wang et al. (2013)
Curcumin	Improved motor coordination & balance from Grid Walk (GW). Improved total neurological composite scores.	↓ brain edema & ipsilateral brain tissue loss & # of MMP +ve cells	Sun et al. (2011)
Minocycline	Improved motor coordination & balance (GW). ↑ locomotion (Open field maze)	↓ brain damage & neuronal death. In vitro: ↓ blood induced neurotoxicity	Xue et al. (2010)
PPAR-γ agonist (Rosiglitazone)	Improved composite NDS assessed from (foot fault, forelimb placing, postural reflex & circling tests). Individual tests not reported.	↑ hematoma resolution & PPAR-γ gene expression ↓ neuronal damage, proinflammatory gene expression, extracellular H_2O_2	Zhao et al. (2007)

Table 2

List of gene and cell based therapies tested in a mouse model of ICH

Stem cells therapies/Transgenics	Behavior	Other Major Effects	References
Collagenase-induced ICH			
Transgenic $CCL2^{-/-}CCR2^{-/-}$ mice	Composite NDS assessed using 28-point neurological deficit scale showed no improvement. Individual tests not reported	↓ hematoma volume, leukocyte, neutrophil infiltration & neuron loss	Yao and Tsirka (2012)
BDNF-transfected 3 T3 fibroblasts	Improved 10-point modified neurologic severity score (nNSS) & performance on Rotarod (RR) test.	↑ neuroblast (Doublecortin +ve) & astrocytes (GFAP +ve) cells ↓ brain tissue loss	Chen et al. (2012b)
hNSCs overexpressing BDNF	Improved performance on RR test & modified limb placing test (MLPT)	↑ BDNF expression, survival of transplanted hNSCs & angiogenesis	Lee et al. (2010)
hNSCs overexpressing Akt1	Improved performance on RR test & MLPT	↑ Akt1 expression, survival & differentiation of transplanted HNSCs	Lee et al. (2009)
hNSCs overexpressing GDNF	Improved performance on RR test & MLPT	↑ GDNF expression survival of transplanted cells & anti-apoptotic proteins ↓ pro-apoptotic proteins	Lee et al. (2009)
hNSCs overexpressing VEGF	Improved performance on RR test & MLPT	↑ VEGF expression & survival of transplanted cells	Lee et al. (2007)
Human neural stem cells (hNSCs)	Improved performance on RR t est & MLPT	↑ survival & differentiation of transplanted cells in perihematomal areas.	Lee et al. (2007)
Transgenic $MMP\text{-}12^{-/-}$mice	Improved performance on single pellet skilled reaching, tape removal & cylinder tasks.	↓ infiltration of microglia/macrophages	Wells et al. (2005)
Blood-induced ICH			
Transgenic TLR4 deficient mice	Improved motor function on cylinder task and ↑ locomotion on open field maze	↓ neuroinflammation in perihematomal areas	Sansing et al. (2011)