Intracerebral haemorrhage: mechanisms of injury and therapeutic targets

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Intracerebral haemorrhage accounts for about 10–15% of all strokes and is associated with high mortality and morbidity. No successful phase 3 clinical trials for this disorder have been completed. In the past 6 years, the number of preclinical and clinical studies focused on intracerebral haemorrhage has risen. Important advances have been made in animal models of this disorder and in our understanding of mechanisms underlying brain injury after haemorrhage. Several therapeutic targets have subsequently been identified that are now being pursued in clinical trials. Many clinical trials have been based on limited preclinical data, and guidelines to justify taking preclinical results to the clinic are needed.

Introduction

Intracerebral haemorrhage is a stroke subtype that is associated with high mortality (about 40% at 1 month),1 and patients who survive typically have major neurological impairments. This disorder accounts for 10–15% of all strokes in the USA, Europe, and Australia and 20–30% of strokes in Asia, with about 2 million cases worldwide per year.2 Although there has been a reduction in overall age-adjusted stroke incidence, findings of a meta-analysis noted that the incidence of intracerebral haemorrhage had not declined between 1980 and 2008.2 As yet, no proven (in phase 3 trials) medical or surgical treatment for intracerebral haemorrhage exists, although surgical decompression for cerebellar haemorrhages is widely accepted as potentially life-saving.3,4

Hypertension is the most common (in about 65% of cases) cause of spontaneous intracerebral haemorrhage, with amyloid angiopathy, brain tumours, aneurysms, arteriovenous malformations, cerebral cavernous malformations, and arteriovenous fistulae also leading to this disorder.4,5 However, intracerebral haemorrhage related to use of anticoagulants is becoming increasingly frequent, now accounting for almost 20% of cases in the USA.6 Most instances of intracerebral haemorrhage are ganglionic (putamen, caudate, and thalamus), followed by lobar, cerebellar, and pontine.1

In addition to symptomatic intracerebral haemorrhage, asymptomatic microbleeds can take place. Findings in healthy adults suggest that these silent cases arise in about 5% of the population,7 and rates of 11–23% of cases have been reported in elderly people.8 About 2 million asymptomatic first cases of intracerebral haemorrhage are estimated in the USA every year.9 The long-term effect of such small bleeds is uncertain. They are a marker for underlying vascular pathological features and a risk factor for further cerebrovascular disease (eg, the presence of microbleeds increases risk for warfarin-associated intracerebral haemorrhage >80-fold).10 Asymptomatic intracerebral haemorrhages might also affect brain function and contribute to vascular dementia and Alzheimer’s disease.11,12

Over the past 20 years, considerable progress has been made in animal and clinical studies to identify mechanisms underlying brain injury induced by intracerebral haemorrhage.13,14,15,16 In this Review, we aim to describe injury mechanisms and potential therapeutic targets and to comment on past and current clinical trials. We also discuss possible guidelines for taking preclinical results to the clinic.

Natural history

Very large haemorrhages (>100 mL) are associated with poor prognosis.7 In human beings, the volume of CSF is about 200 mL17 with large haemorrhages and associated perihematomal oedema, therefore, displacement capacity is exhausted. With smaller haemorrhages, most patients survive the initial ictus but haematoma-induced secondary brain injury can result in severe neurological deficits and death.1 In about 20–40% of cases, haematoma expansion takes place during the first day after the initial ictus, contributing to the mass effect of the intracerebral haemorrhage, and such expansion is a predictor of a poor outcome.18–21 A rim of oedema also forms around the haematoma, adding to the mass effect and brain injury.22 Oedema increases rapidly after intracerebral haemorrhage and peaks in about the second week after ictus (figure 1).22–24 The haematoma gradually resolves over several weeks, usually leaving a cavity where brain tissue has been destroyed (figure 2).22

The location of an intracerebral haemorrhage is important for determination of outcome and potential treatment. Pontine haemorrhages have the highest mortality, and superficial haemorrhages might be more amenable to surgical removal.22 Depending on location, bleeding from an intracerebral haemorrhage could extend into the ventricular system. Such intraventricular haemorrhages arise in about 40% of cases and predict a poor outcome.25

Seizures take place in about 8% of patients after intracerebral haemorrhage, mostly (about 90%) within the first 3 days.26 Results are conflicting about the effect of such seizures on clinical outcome.27

Animal models

The main models used to study intracerebral haemorrhage entail direct injection of either blood or
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collagenase into different brain areas in rodents and larger species such as pig.25,26 Blood injection mimics the effects of an intracerebral haematoma but does not have disrupted vasculature as the source. Collagenase injection does disrupt vasculature, but the enzyme could have other effects unrelated to haemorrhage and it might cause disruption of several blood vessels, including capillaries. Thus, cautious interpretation of results in animals is needed, since differences in the relative importance of injury mechanisms are apparent between the two model types.25 Other less frequently used models are available, including the spontaneously hypertensive stroke-prone rat and hypertension-related mouse models developed by Heistad’s group.27,28 Similarly, a model of Alzheimer’s disease in mice results in haemorrhage.29

Recent advances have been made in examination of known risk factors for intracerebral haemorrhage in human patients using animal models. For example, work done with the blood-injection model shows that brain injury is worse in aged than in young rats.16 Furthermore, in a collagenase mouse model, use of warfarin causes an increase in intracerebral haemorrhage.31,32

For ischaemic stroke, considerable debate has taken place about the use of animal models.33 Up to now, no preclinical studies have led to a successful phase 3 clinical trial in intracerebral haemorrhage. However, the situation with intracerebral haemorrhage is somewhat different from that with ischaemic stroke, in terms of the number of clinical trials that have been undertaken. Moreover, many trials of intracerebral haemorrhage were not based directly on preclinical data (eg, haematoma evacuation and prevention of haematoma expansion trials) or were based mainly on preclinical findings from animal models of conditions other than intracerebral haemorrhage, such as ischaemic stroke. Thus, clinical trials of dexamethasone, mannitol, and glycerol34–36 were undertaken largely on the basis of oedema reduction in other neurological disorders, and clinical trials of disufenton37 and gavestinel38 were done on the basis of preclinical findings in models of ischaemic stroke. Ongoing clinical trials to test agents that have undergone further preclinical testing will provide more information on the use of animal models of intracerebral haemorrhage.

Primary brain injury

The initial bleed after brain injury causes physical disruption to the brain’s cellular architecture. The haematoma’s mass can increase intracranial pressure (mass effect), subsequently compressing brain regions and thereby potentially affecting blood flow (ischaemia) and leading to brain herniation. Several strategies have been investigated to lessen morbidity after primary injury.

Clot removal

Because of the physical effects of the haematoma (mass effect), many clinical trials have examined the effect of clot removal. As yet, surgical evacuation has not been shown to be beneficial,39 possibly because the adverse effects of surgery negate the benefit of the evacuation. Two potential approaches are currently under investigation in the STICH II4 and MISTIE40 clinical trials, the findings of which could limit adverse surgical effects (table, figure 3). In STICH II, only superficial (<1 cm from the cortical surface) lobar haemorrhages are being evacuated;41 and in MISTIE, a minimally invasive approach with tissue plasminogen activator to assist evacuation is being used. A surgical evacuation trial is also taking place in China (SATIH trial; ClinicalTrials.gov identifier NCT00752024); and in the USA, a trial of lysis

Figure 1: CT scan of a patient with perihaematomal oedema (hypodensity zone) 14 days after intracerebral haemorrhage
Note striking perihaematomal oedema with midline shift (arrows).

Figure 2: CT scan of a patient with pronounced brain tissue loss (atrophy) at day 90 after intracerebral haemorrhage
Note dilated ipsilateral ventricle (asterisk), fluid-filled cavity (arrow), and enlarged sulci (arrowhead).
with ultrasound (SLEUTH trial) is underway. Location of the intracerebral haemorrhage is important for outcome, and surgical decompression is widely accepted as potentially life-saving for cerebellar haemorrhage. Two clinical trials have focused on haematoma expansion.

### Haematoma expansion

A subset of patients with intracerebral haemorrhage undergoes haematoma expansion within the first day after ictus. Prevention of such expansion could, therefore, be a strategy to limit mass effect (and secondary injury). Two types of clinical trial have focused on haematoma expansion.

First, agents that alter the coagulation cascade or fibrinolysis have been studied. Findings of early factor VIIa trials showed promise in terms of reduction of haematoma expansion; however, final outcome was not improved in patients. Use of factor VIIa is associated with an increased rate of thromboembolic complications. Therefore, studies have focused on ascertaining which patients might benefit best from factor VIIa administration, either because of evidence of haematoma expansion with the spot sign (eg, STOP-IT [NCT00810888] and SPOTLIGHT [NCT01359202] trials) or because patients were on anticoagulants or antiplatelet drugs at the time of intracerebral haemorrhage (NCT00222625).

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**Table: Current and past clinical trials for intracerebral haemorrhage**
Other similar approaches that are being tested clinically are use of platelet transfusions for patients on antiplatelet treatment (PATCH trial) and use of the antifibrinolytic agent aminocaproic acid (ATICH trial). In a trial of 45 patients, Naidech and colleagues reported some benefit of early platelet transfusion in patients with intracerebral haemorrhage with low platelet activity or who were known to have received antiplatelet treatment.

A few preclinical studies have been done on the effect of haematoma expansion. Kawai and co-workers noted that factor VIIa could reduce early haematoma growth in a rat collagenase model. Collagenase-induced intracerebral haemorrhage is under investigation in warfarin-treated animals. Illanes and colleagues studied the effects of different methods of reversal of warfarin anticoagulation on collagenase-induced intracerebral haemorrhage in mice and found that treatment with prothrombin complex concentrate and frozen plasma resulted in smaller haemorrhages, whereas factor VIIa and tranexamic acid had less effect.

The second approach to prevention of haematoma expansion is lowering of blood pressure—eg, in the INTERACT, ICH ADAPT, and ATACH trials. Whether findings of these studies will show long-term therapeutic benefit is unknown, but evidence of reduced haematoma expansion has been reported.

Few preclinical assessments have been done of the effects of blood pressure on haematoma expansion. Wu and colleagues reported no difference in haemorrhage volume between spontaneously hypertensive rats and normotensive control rats after collagenase injection. However, the spontaneously hypertensive rats had greater intracerebral haemorrhage-induced brain injury than the controls, suggesting that hypertension could have effects on brain injury induced by intracerebral haemorrhage other than by modification of haematoma volume. Acute changes in blood pressure (rather than prolonged hypertension) could possibly be more important in haematoma expansion. Benveniste and co-workers examined intracerebral haemorrhage after brain biopsy and noted no difference in haemorrhage volume between spontaneously hypertensive rats and normotensive controls, but they recorded increased haemorrhage in normotensive control rats that were subjected to acute increases in blood pressure.

An alternative approach to reduction of haematoma expansion was suggested by Liu and colleagues, who reported that plasma kallikreins inhibit platelet aggregation. Thus, haematoma expansion could be reduced by inhibition of plasma kallikreins or by a deficiency in these enzymes.

### Ischaemia

The extent to which perihaematoma ischaemia takes place after intracerebral haemorrhage is still controversial. With very large haematomas, intracranial pressure will rise, the brain will herniate, and blood flow will fall. If tissue supplied by the vessel that ruptures has insufficient collateral supply and the vessel loses patency, this loss of patency might also cause some drop in blood flow. However, with a few exceptions, findings of several clinical and animal studies have not shown changes in perihematomal blood flow to levels expected to cause ischaemic damage. Interpretation of blood flow in perihematomal tissue is complicated by changes in metabolism and oedema formation. Thus, for example, Zazulia and colleagues noted that cerebral blood flow and the cerebral metabolic rate for oxygen were both decreased in the perihematomal zone, resulting in a reduced oxygen extraction fraction. These findings suggest that a zone of hypoperfusion without ischaemia exists. Data indicate that declines in cerebral metabolism could reflect mitochondrial damage rather than ischaemia. The effect of oedema on blood flow should also not be underestimated. Wagner and colleagues reported that perihematomal water content in the white matter of pigs rose from 73% to 86%. In terms of water content (g/g dry weight), this increase represents a 127% change, and tissue swelling was 93%.

### Secondary brain injury

Secondary injury after intracerebral haemorrhage could be caused by a cascade of events initiated by the primary injury (eg, mass effect and physical disruption), by the physiological response to the haematoma (eg, inflammation), and by release of clot components (eg, platelet aggregates). Surgical removal of haematoma and prevention of haematoma expansion could potentially reduce injury by affecting several downstream mechanisms. Pioglitazone accelerates haematoma resolution in rodents but has not been shown to reduce haematoma expansion in clinical trials.
Thrombin can affect many cell types, including brain endothelial cells (leading to disruption of the blood-brain barrier and formation of brain oedema), neurons and astrocytes (which thrombin can kill at high concentrations in vitro), and microglia (which are activated by thrombin). Thrombin can also initiate potentially harmful pathways such as apoptosis in cultured neurons and astrocytes, and can activate Src kinase, which might contribute to excitotoxicity, vascular hyper-permeability, and inflammation.

Findings suggest that inhibition of thrombin can reduce injury induced by intracerebral haemorrhage. Furthermore, perihematomal brain oedema was diminished after systemic treatment with argatroban, a thrombin inhibitor. This study, drug administration was only started 24 h after the haemorrhage, to prevent rebleeding.

Although high concentrations of thrombin can mediate brain injury after intracerebral haemorrhage, low concentrations are neuroprotective. Thus, the effect of thrombin could depend on the size of the haematoma and proximity of thrombin to the haematoma. Moreover, thrombin has a reported role in brain recovery and neurogenesis after intracerebral haemorrhage.

Although thrombin is most known for cleavage of fibrinogen to fibrin, other effects are mediated by three protease-activated thrombin receptors, PAR1, PAR3, and PAR4. Expression of thrombin receptor mRNA is seen in neurons and astrocytes, and immunoreactivity of the thrombin receptor has been reported in human brain tissue. Findings suggest that PAR1 mediates some pathological effects of thrombin and plays a part in pathophysiological events induced by intracerebral haemorrhage.

Inflammation

A pronounced inflammatory reaction takes place after intracerebral haemorrhage, with activation of resident microglia, an influx of leucocytes into the brain, and production of inflammatory mediators. Findings from several animal studies suggest that inflammation has an important role not only in brain injury after intracerebral haemorrhage but also in brain recovery. The effect of modulation by inflammation on brain injury caused by intracerebral haemorrhage has yet to be ascertained.

Microglia are activated in the brain after intracerebral haemorrhage in animal models. This response takes place early (starting at about 1 h), peaks after 3–7 days, and persists for 3–4 weeks. A benefit of inhibition of microglia activation with tuftsin or minocycline has been noted after intracerebral haemorrhage in some studies, but not all. However, as with cerebral ischaemia, the effects of microglia on brain injury after intracerebral haemorrhage could be both detrimental and beneficial (eg, clot resolution), and the net effect might be time-dependent.

Neutrophils are the earliest leucocytes to enter the brain after intracerebral haemorrhage. They seem to contribute to brain injury by producing reactive oxygen species and proinflammatory proteases and disrupting the blood-brain barrier. Monocytes also enter the brain from the bloodstream after intracerebral haemorrhage, and depletion of neutrophils from the infiltrate reduces monocyte entry. The toll-like receptor 4 on leucocytes seems to be important for infiltration of both neutrophils and monocytes.

Two cell types that have received little attention in intracerebral haemorrhage are resident mast cells and infiltrating lymphocytes. Both have a role in intracerebral haemorrhage-induced injury. As with ischaemic stroke, the role of these cells deserves further investigation.

In both animals and people, intracerebral haemorrhage is associated with upregulation of various inflammatory mediators in the brain, including cytokines—such as tumour necrosis factor α and interleukin 1β—chemokines, adhesion molecules, and matrix metalloproteinases—such as MMP9 and MMP3. Evidence indicates that these inflammatory mediators are involved in brain injury induced by intracerebral haemorrhage in animals.

Breakdown of the blood-brain barrier takes place after intracerebral haemorrhage. This process might contribute to inflammation by promotion of leucocyte infiltration but could itself be a result of inflammation, since leucocyte-derived reactive oxygen species, proinflammatory cytokines, chemokines, and MMPs have all been implicated in disruption of the blood-brain barrier. As well as promoting inflammation, blood-brain barrier disruption contributes to the formation of vasogenic oedema after intracerebral haemorrhage.

The cyclo-oxygenase inhibitor celecoxib has been investigated for intracerebral haemorrhage in the ACE-ICH pilot clinical trial, but the results have yet to be reported (NCT00526214). Another agent that has anti-inflammatory actions, pioglitazone, is currently being studied in a phase 1 clinical trial for intracerebral haemorrhage (SHRINC), although this drug has many effects other than on inflammation. Similarly, two statins that have anti-inflammatory actions in addition to other...
effects have been tested in clinical trials. In a preliminary trial of rosuvastatin, a positive effect was noted, but a simvastatin trial was closed because of poor enrolment (NCT00718328).

Complement

The complement system is involved in immune reactions, including cell lysis and the inflammatory response. Plasma protein components of the complement system are typically excluded from the brain by the blood-brain barrier, but they can enter the brain after intracerebral haemorrhage either as part of the haemorrhage or after breakdown of the blood-brain barrier. Complement activation and formation of the membrane attack complex (consisting of C5b-9) has been noted in the brain after intracerebral haemorrhage. The membrane attack complex plays a part in erythrocyte lysis and could, therefore, be implicated in haemoglobin and iron release, resulting in perihematomal tissue damage (figure 4). Moreover, the membrane attack complex might induce direct injury in perihematomal neurons, glia, and blood vessels. Complement cascade activation also produces C3a and C5a, which are powerful chemoattractants for leucocytes and activators of microglia and mast cells, which can enhance the inflammatory response to intracerebral haemorrhage. Inhibition of the complement cascade by depletion of components, antagonists, or gene knockout reduces intracerebral haemorrhage-induced brain injury. However, some data about C5 are conflicting, with a C5a inhibitor being protective but C5-deficient mice showing augmented brain injury after intracerebral haemorrhage. This difference could reflect compensatory changes in response to C5 loss in the deficient mice. As with the inflammatory system, although complement activation can enhance brain injury early after intracerebral haemorrhage, the complement cascade might also have beneficial effects on long-term brain repair.

Haemoglobin, iron, and free radicals

Mounting evidence suggests that haemoglobin and iron release from the haematoma is a major contributor to brain injury induced by intracerebral haemorrhage (figure 4). Intracerebral injection of lysed erythrocytes into rodent brain causes brain injury, which is mimicked by infusion of haemoglobin and iron. After intracerebral haemorrhage, iron builds up in tissue around the haematoma (figure 5). An iron chelator—deferoxamine—reduced brain injury induced by intracerebral haemorrhage in rats and pigs (figure 6). Although little or no protection was noted in collagenase models. Deferoxamine is currently being tested in a clinical trial for intracerebral haemorrhage. Inhibitors of haem oxygenase, an enzyme that releases iron from haem, or deletion of haem oxygenase 1, also reduce brain injury after intracerebral haemorrhage.

One mechanism by which iron might cause tissue damage is by generation of free radicals. Free radical-mediated damage has been noted after intracerebral haemorrhage, and scavengers of free radicals lessen intracerebral haemorrhage-induced injury in animals. However, free radicals could arise from many sources after intracerebral haemorrhage.
radical spin-trap agent, was investigated in patients with intracerebral haemorrhage as part of the CHANT trial, but no benefit was seen. Reasons for this negative outcome are uncertain but could reflect insufficient permeability of the blood-brain barrier or an inability to neutralise the high amounts of free radicals produced after intracerebral haemorrhage.

Other blood components
Although haemoglobin is the major intracellular component of erythrocytes, it is not the only one. In rats, intracerebral injection of carbonic anhydrase 1, another component of erythrocytes, caused brain injury, and treatment with a carbonic anhydrase inhibitor reduced intracerebral haemorrhage-induced injury.

Glutamate
Glutamate-induced excitotoxicity has a major role in cell death after cerebral ischaemia, and some evidence shows that glutamate can also participate in brain injury after intracerebral haemorrhage. However, some underlying mechanisms could be specific for intracerebral haemorrhage. The initial bleed leads to an influx of glutamate from the bloodstream, and production of thrombin after haemorrhage results in Src kinase activation, which phosphorylates NMDA receptors and augments their function. By contrast with cerebral ischaemia, glutamate receptor antagonists have not been investigated in human intracerebral haemorrhage apart from in one small trial with the NMDA antagonist CP-101,606, in which traumatic brain injury was the main focus.

Seizures
Clinical and subclinical seizures arise in about 8% and 30%, respectively, of patients with intracerebral haemorrhage. The causes of such seizures are unknown, and animal studies of seizures induced by intracerebral haemorrhage are sparse. However, seizures might be related to increased amounts of extracellular glutamate and downregulation of GABA and potassium channels after intracerebral haemorrhage. Moreover, intracerebral thrombin can elicit seizure activity in rats. Whether seizures affect outcome after intracerebral haemorrhage is debatable.

Spreading depression
Waves of spreading depression have been reported in a pig model of intracerebral haemorrhage and in more than 60% of patients with intracerebral haemorrhage. The role of spreading depression in ischaemic injury has attracted much interest, because the energy needed to repolarise might compromise already damaged and energy-depleted cells. The effect of spreading depression on perihematomal and more distant cells after intracerebral haemorrhage has received very little attention and deserves more investigation.

Cell-death pathways
Intracerebral haemorrhage results in perihematomal cell death and brain atrophy. Cell-death pathways involved seem to be a mixture of necrosis and apoptosis, although the predominant process is unknown. Various approaches have been used to reduce apoptosis and brain injury in animal models of intracerebral haemorrhage. Taurourodeoxycholic acid, an anti-apoptotic compound, is currently being tested in a clinical trial. Citicoline, a membrane stabilisation agent, is also under investigation. Autophagy might also take place after intracerebral haemorrhage, although whether this pathway is detrimental or beneficial is unclear.

Endogenous defence mechanisms
After intracerebral haemorrhage, various endogenous proteins are upregulated, which could protect the brain from the injury mechanisms described above. For example, iron-handling proteins such as ferritin are strongly upregulated. Nuclear factor erythroid 2-related factor 2 (Nrf2), a transcription factor that responds to oxidative stress, might be involved in the regulation of some antioxidant defence mechanisms. Wang and colleagues reported that brain injury after...
collagenase-induced intracerebral haemorrhage was enhanced in Nrf2-knockout mice.

The use of drugs to upregulate defence mechanisms has attracted considerable interest. Nrf2 can be upregulated by several agents, including sulforaphane, which protects against intracerebral haemorrhage-induced brain injury in mice and rats via a Nrf2-dependent mechanism. Peroxisome proliferator-activated receptor γ (PPARγ) agonists might also exert some of their benefit after intracerebral haemorrhage by upregulation of cellular defence mechanisms, including catalase.

Pluripotent agents

Some agents in preclinical trials have several actions, which could be beneficial for intracerebral haemorrhage. For example, minocycline acts as an iron chelator and an inhibitor of microglial activation, and pioglitazone affects haematoma resolution and upregulates endogenous defence mechanisms. Erythropoietin, albumin, and statins are other pluripotent agents that reduce intracerebral haemorrhage-induced brain damage in animal models. Agents with more than one protective effect are attractive as potential therapeutic agents, and some are in clinical trials—eg, pioglitazone (SHRINC) and albumin (ACHIEVE; NCT00990509).

Hypothermia is a standard therapeutic approach that affects many treatments and has been studied in animal models of intracerebral haemorrhage. Prolonged mild hypothermia improved functional recovery and brain oedema without affecting lesion size in the rat. A clinical trial is ongoing to investigate use of ibuprofen to aggressively lower temperature in patients with intracerebral haemorrhage and fever (NCT01530880).

Brain recovery after intracerebral haemorrhage

If patients survive the early days after an intracerebral haemorrhage, gradual clot resolution takes place, and they might recover some neurological function, although this recovery is almost always incomplete. Improvement of function could entail clot resolution, subsidence of the acute injury (eg, reduced oedema), neuronal plasticity with surviving neurons (including the contralateral hemisphere) taking on new functions, and possibly neurogenesis. Recovery of function can be pronounced, as in rodent models of intracerebral haemorrhage.

Various methods have been used preclinically to enhance the process of recovery after intracerebral haemorrhage. Microglia and blood-derived macrophages play a part in clearance of extravasated erythrocytes by phagocytosis, thereby limiting release of potentially toxic lysate products into the extracellular space (figure 4). Zhao and colleagues have enhanced this phagocytosis process by administration of the PPARγ agonists rosiglitazone and pioglitazone. These agents accelerate haematoma resolution and reduce deficits induced by intracerebral haemorrhage in rodents.

The use of rehabilitation to maximise neurological recovery has also been widely studied. In rats with intracerebral haemorrhage, forced running had no effect on outcome, but delayed exposure to an enriched environment and skilled reach training both improved neurological outcome and reduced lesion volume. This improvement was associated with increased dendritic complexity rather than neurogenesis.

As for ischaemic stroke, the idea that stem cells might improve outcome after intracerebral haemorrhage has attracted much interest. Seyfried and co-workers reported that, after intracerebral haemorrhage in rats, bone-marrow cells injected intravenously migrated to the lesion site and improved neurological outcome. One factor that could restrict the effect on outcome of exogenous stem cells is cell survival. Lee and colleagues noted that genetically modifying human neural stem cells to overexpress Akt1 increased their survival in a mouse model of intracerebral haemorrhage and enhanced their protective effects on the brain. A clinical trial is ongoing in China to investigate the effects of stem-cell transplantation in patients with intracerebral haemorrhage (NCT01389453).

Future directions

In the past two decades, a striking increase in the amount of preclinical and clinical research on intracerebral haemorrhage has been seen. This work has resulted in much new information about injury mechanisms and potential therapeutic targets. However, these data have yet to result in any treatment for intracerebral haemorrhage. The mechanisms believed to play a part in brain injury induced by intracerebral haemorrhage differ in type, magnitude, and timing from those for ischaemic stroke. These differences should be taken into account when designing clinical trials. In the past, in some cases, very little published preclinical evidence in intracerebral haemorrhage has been available before a drug has been tested in patients (eg, dexamethasone, gavestinel [a glycin antagonist], and mannitol). Indeed, while many complaints have been made about animal models of cerebral ischaemia failing to predict therapeutic efficacy, only very recently have clinical trials in intracerebral haemorrhage been based on preclinical testing. Time will tell about the use of preclinical models of intracerebral haemorrhage for informing clinical trials.

Search strategy and selection criteria

This Review focuses on research in intracerebral haemorrhage between January, 2005, and April, 2012. We searched Medline with the terms “intracerebral haemorrhage” and “intracerebral haematoma” and retrieved all articles published in English. We selected articles for their conceptual importance and primacy. For controversial issues, evidence on both sides was sought.


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