Interleukin-1 in Stroke
From Bench to Bedside

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Inflammation is a host defense response to infection that normally culminates in pathogen removal and tissue repair. In the absence of a pathogen, sterile inflammation occurs, which is now recognized as a major contributor to noncommunicable disease (ie, cardiovascular diseases, cancers, chronic respiratory diseases, and diabetes mellitus). Although several regulatory molecules are implicated in inflammation, a key central role is provided by members of the interleukin-1 (IL-1) family, important mediators of the innate immune response. Here, we provide an overview of the basic biology of IL-1, before going on to describe both the preclinical and the clinical evidence that suggest IL-1 to be a major therapeutic target in all forms of stroke, including details of completed and ongoing clinical trials. It should be noted that in compiling this review, a full systematic search strategy was not used and that any negative data are likely limited by publication bias.

IL-1 Family

Although 11 members of the IL-1 family have been described, the most important of these and most studied in the context of stroke are the agonists IL-1α and IL-1β, and the IL-1 receptor antagonist (IL-1Ra). Both IL-1α and IL-1β are created as 31-kDa precursor proteins that undergo enzymatic cleavage to bioactive 17-kDa forms, although they differ in that pro–IL-1α possesses some biological activity, whereas pro–IL-1β is completely inactive. Cleavage of IL-1β is classically achieved via caspase-1 (or IL-1–converting enzyme), activity of which is triggered via the activation of the inflammasome, an intracellular protein complex. Inflammasome activation in sterile inflammation is triggered by damage-associated molecular patterns, which are released by necrotic cells within the ischemic brain. Pro–IL-1β can also be cleaved to the active 17-kDa form by the action of neutrophil serine proteinases, including proteinase 3 and elastase. Given the contribution of neutrophils to ischemic brain damage, these cells could provide an additional/alternative source of mature IL-1β in stroke. Proteolytic cleavage of IL-1α typically occurs through the actions of calpain, a membrane-associated calcium-dependent cysteine-protease, although the inflammasome can also be involved.

Both IL-1α and IL-1β induce their biological effects through binding to the IL-1 type I receptor (IL-1R1), which is expressed on several cell types. Successful signal transduction requires association of the ligand–IL-R1 complex with the IL-1 receptor-accessory protein. The IL-1/IL-1R1/IL-1 receptor-accessory protein signaling complex is extremely sensitive, early reports suggesting activity in some systems with <10 receptors/cell occupied. IL-1Ra is a naturally occurring molecule that acts as a competitive inhibitor of IL-1α and IL-1β by binding to IL-1R1 without inducing an intracellular signal. IL-1Ra is a highly specific inhibitor and robustly blocks all known actions of IL-1, thereby providing an extremely powerful experimental tool as well as effective therapeutic agent. It should be recognized, however, that to effectively block IL-1 responses, IL-1Ra needs to be present in 100- to 1000-fold molar excess, because of the relatively high expression of IL-1R1 on cells and need for only a few receptors to be occupied to trigger a full response. Importantly, no agonist activity of IL-1Ra is observed even when administered at doses a million-fold higher than that required to see effects with IL-1α and IL-1β. Further control of the IL-1 system is offered by the IL-1R2, to which both IL-1α and IL-1β bind with high affinity and which acts as a decoy receptor because of the absence of an intracellular signaling domain. Recent data also demonstrate that IL-1R2 binds to IL-1α in the cytosol, preventing its interaction with IL-1R1 on release from necrotic cells. The multiple pathways available to regulate IL-1 activity signify its biological importance.

IL-1 is a pleiotropic cytokine with a multitude of biological effects described in numerous cell types, many of which are relevant in the context of stroke risk and outcome. Downstream effects of IL-1 include increased expression of cytokines, chemokines and growth factors, activation of matrix metalloproteinases, upregulation of adhesion molecules, increased leukocyte infiltration, platelet activation, alterations in blood flow, increased angiogenesis, decreased...
neurogenesis, and a plethora of other effects. Detailed discussion of all these effects and mechanisms involved is beyond the scope of this article but can be found in recent reviews.\textsuperscript{14,15}

**IL-1 and Stroke: Preclinical Evidence**

Evidence of a role for IL-1 in cerebral ischemia derives mainly from preclinical studies in ischemic stroke that have shown it to be a key mediator of neuronal damage (Figure), with more limited evidence available from studies of both intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH).

**Ischemic Stroke**

The first evidence suggesting a role for IL-1 in stroke came from studies in the 1990s where treatment with recombinant IL-1Ra in rats undergoing permanent middle cerebral artery occlusion (MCAO) was shown to be protective, after central\textsuperscript{16} or peripheral\textsuperscript{17} administration. In a temporary MCAO (tMCAO) model in rats intracerebroventricular injection of an anti–IL-1β antibody was also found to reduce ischemic injury.\textsuperscript{18} Subsequently, delayed (30 minutes) administration of IL-1Ra (intracerebroventricular) in rats was shown to reduce infarct volume after permanent MCAO.\textsuperscript{19} Interestingly, the delayed protective effect of IL-1Ra was not seen with peripheral treatment in permanent MCAO, although dose-dependent protection with administration at time of occlusion was observed.\textsuperscript{20} Protective effects of IL-1Ra in a mouse model of permanent MCAO were reported for the first time shortly after.\textsuperscript{21} In the same year, Hara et al\textsuperscript{22,23} used newly described IL-1–converting enzyme inhibitors and dominant-negative IL-1–converting enzyme–expressing transgenic mice to show that blocking cleavage of pro–IL-1β is neuroprotective after tMCAO. The availability of transgenic mice allowed further evidence to be accrued to support a role for IL-1 in stroke, with mice deficient in both IL-1α and IL-1β showing marked reductions (≈80%) in lesion volume.\textsuperscript{24,25} Mice lacking IL-1R1 showed similar levels of ischemic injury to the wild-type control after MCAO\textsuperscript{26} although protection was seen with milder forms of hypoxia–ischemia.\textsuperscript{27} Interestingly, exogenous IL-1β was able to increase the infarct volume in IL-1R1–deficient mice, suggesting the existence of a novel IL-1 receptor.\textsuperscript{26} This apparent non–IL-1R1 signaling has now been shown to be because of the presence of a truncated signaling receptor (termed IL-1R3) in this particular strain of IL-1R1–deficient mice.\textsuperscript{28} We have recently generated floxed-IL-1R1 mice that lack all known IL-1 receptors, which will allow confirmation of the role of IL-1R1 in stroke and more importantly the cell type that mediates IL-1 actions.\textsuperscript{29}

In the early years of the new millennium, there were, in comparison with a decade previously, fewer investigations of IL-1 inhibition in stroke. Although one of these studies did report that delayed (3 hours) administration of IL-1Ra still provided protection after tMCAO in the rat, this was still with central (intracerebroventricular) delivery.\textsuperscript{30} A similar study with a highly selective caspase-1 inhibitor showed it also to be effective with delayed (3 hours) administration, efficacy being lost at 6 hours.\textsuperscript{31}

A meta-analysis and systematic review of the effectiveness of IL-1Ra in ischemic stroke was published in 2009. This confirmed protective effects (≈38% reduction in infarct volume) but highlighted the lack of studies using systemic administration, delayed treatment, or in animals with clinically relevant comorbidities.\textsuperscript{32} Recent work has addressed these concerns, confirming efficacy of IL-1Ra after delayed subcutaneous administration in corpulent rats (a model of metabolic syndrome)\textsuperscript{33} and showing that IL-1Ra can reverse exacerbating effects of acute infection (pneumonia) in both mice and rats.\textsuperscript{34} Furthermore, it is clear that IL-1Ra can reach the brain at therapeutic doses after systemic administration after tMCAO in the rat.\textsuperscript{35} Systemic administration of IL-1Ra also provides long-term functional recovery after MCAO.\textsuperscript{36}

Most recently, a cross-laboratory study of IL-1Ra confirmed the protective effects of IL-1Ra, reported for >20 years.\textsuperscript{37} This study comprised evaluation of the effects of IL-1Ra in 8 separate experiments performed in 5 individual centers, rather than a multicenter study as recently performed for anti--CD49d treatment.\textsuperscript{38} Experimental design was heterogeneous in that transient (filament, thrombin) and permanent (distal occlusion) models of MCAO were used, with infarct volume (assessed by histology or magnetic resonance imaging) and behavior as outcomes. Meta-analysis of the individual studies

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**Figure.** Mechanisms of interleukin-1 (IL-1) action in stroke. Stroke-related comorbidities and risk factors are associated with a raised systemic inflammatory profile, mediated in part by IL-1. Post-stroke increases in IL-1 in the brain mediate detrimental (indicated in red) inflammatory processes in the acute phase that contribute to worse outcome. In the subacute and chronic phase after stroke, certain actions of IL-1 may be beneficial (indicated in green). Figure provided and used with permission courtesy of Christopher Hoyle, University of Manchester, United Kingdom. MMP indicates matrix metalloproteinases; and TNF, tumor necrosis factor.
showed IL-1Ra to reduce lesion volume, neurological deficits, and functional outcome (to day 7 but not day 28). In addition, the effects of tissue-type plasminogen activator on the efficacy of IL-1Ra in filament and thrombin models were investigated, protective effects being sustained. How IL-1Ra impacts thrombolytic therapy has not been investigated either experimentally or clinically. Given increasing the use of thrombolysis and the introduction of intravascular therapy studies on adjunct treatment with IL-1Ra are urgently needed, as this may help limit damaging inflammatory responses and extend the time window for use.

Additional support of a role for IL-1 in ischemic injury is derived from early studies demonstrating that administration of recombinant IL-1 exacerbated damage,\textsuperscript{18,19} as did blockade of endogenous IL-1Ra through intracerebroventricular delivery of an IL-Ra antiserum.\textsuperscript{39} Later, more extensive studies show that systemic administration of IL-1 just before tMCAO significantly worsens outcome in both mice and rats through neutrophil- and platelet-dependent mechanisms that restrict reperfusion.\textsuperscript{40–42}

Alongside studies reporting neuroprotective effects of inhibition of endogenous IL-1 and exacerbating effects of exogenous IL-1, there are many reports describing decreases in expression of IL-1 and IL-1Ra at both the gene and the protein level in response to ischemic stroke in various experimental models.\textsuperscript{40,41}

Mechanisms underlying beneficial effects of IL-1Ra in stroke remain to be fully elucidated although data exist to suggest both neuroprotective and vasculoprotective actions. Direct neuroprotective effects of IL-1Ra are seen after administration with excitotoxins in the rat brain,\textsuperscript{43} whereas vascular actions are suggested by the prevention of blood–brain barrier breakdown and neutrophil migration.\textsuperscript{44}

**Subarachnoid Hemorrhage**

Preclinical studies have identified the importance of IL-1 in post-SAH inflammation.\textsuperscript{44–48} IL-1 has been shown to be induced in the brain and cerebrospinal fluid (CSF) after SAH and may contribute to neuronal damage in several ways. IL-1 may cause upregulation of endothelin, a potent vasoconstrictor, directly causing vasospasm.\textsuperscript{49} IL-1 exacerbates blood–brain barrier breakdown and therefore edema, which may cause increased intracranial pressure.\textsuperscript{50} Animal models of posthemorrhagic vasospasm have demonstrated elevated levels of IL-6 (in arteries exposed to hemorrhage),\textsuperscript{51,52} which are known to be upregulated by IL-1. Based on this evidence, the inhibition of inflammatory cytokines has been proposed as a strategy for treating post-SAH vasospasm and thus preventing delayed cerebral ischemia,\textsuperscript{53} as well as effects of the primary bleed. Greenhalgh et al\textsuperscript{57} showed that the red cell breakdown product heme acts as a damage-associated molecular pattern, driving IL-1-α-dependent inflammation after SAH.\textsuperscript{55} In the same study, administration of IL-1Ra in the filament rupture model of SAH reduced blood–brain barrier disruption, the extent of which correlated with a reduction in neuronal damage.

**Intracerebral Hemorrhage**

Although ICH presents to clinicians in a similar manner to ischemic stroke, the underlying pathophysiology is different in many ways. Rapid extravasation of blood causes immediate tissue injury and is followed by secondary injury over the subsequent hours to days, driven by a cascade of cellular and molecular events including the toxic effects of blood components (thrombin, heme, and iron) and inflammation. Despite different factors initiating the inflammatory response to ICH, there is evidence to suggest that IL-1 is a key mediator. IL-1β is rapidly upregulated in perihematomatol brain tissue 24 hours after striatal autologous blood injection in rats, with levels of IL-1β mRNA increased around 40-fold in the striatum and 20-fold in the overlying cortex, when compared with sham animals (striatal injection of saline).\textsuperscript{53} Further work in the collagenase ICH model in rats has confirmed this rapid upregulation of IL-1β and shown that it peaks at around 6 hours (30-fold greater than sham) and remains significantly upregulated as late as day 7 (5-fold greater than sham).\textsuperscript{54} Upregulation of endogenous IL-1Ra in rats leads to a reduction in edema 24 and 72 hours after striatal autologous blood injection into the striatum as well as reducing edema and polymorphonuclear leukocyte infiltration 24 hours after thrombin injection.\textsuperscript{54} These findings demonstrate that IL-1 is rapidly upregulated in animal models after ICH and that it promotes polymorphonuclear leukocyte infiltration and worsens cerebral edema.

**IL-1 in Stroke: Clinical Evidence**

**Expression of IL-1 and Other Inflammatory Mediators**

Several studies have demonstrated elevated concentrations of the proinflammatory cytokines IL-1 and IL-6 in the CSF of patients with acute ischemic stroke or with SAH.\textsuperscript{55–59} suggesting a localized central nervous system inflammatory response to ischemic injury. Levels of IL-1β and IL-6 in ischemic stroke or aneurysmal SAH have been consistently shown to be lower in serum compared with CSF suggesting intrathecal derivation of these proinflammatory mediators,\textsuperscript{57} most likely driven by the severity of ischemic injury.\textsuperscript{60} Furthermore, induction of peripheral IL-1 in whole blood ex vivo, along with other classical innate cytokines, is suppressed\textsuperscript{60} after ischemic stroke, suggesting downregulation of innate immune cellular responsiveness, or a switch to a peripheral anti-inflammatory state. The extent of suppression of IL-1 induction correlates inversely with plasma cortisol concentrations and infarct volume. By contrast, IL-1Ra and IL-6 are released into the peripheral circulation and plasma concentrations are elevated in acute stroke,\textsuperscript{60} correlating positively with infarct volume. A plausible explanation for these observations is that the extent of central nervous system tissue injury drives IL-1 induction, which in turn induces the expression of IL-1Ra and mediates suppression of peripheral blood IL-1 induction, perhaps via activation of the hypothalamic-pituitary-adrenal axis.

Upregulation of IL-1 has been demonstrated in the analyses of human perihematomatol brain within 24 hours of symptom onset, using specimens obtained during surgery to evacuate the hematoma.\textsuperscript{61} Other clinical studies in ICH have
focused on peripheral inflammatory markers and shown associations between fever, elevated white blood cell count, IL-6, C-reactive protein (CRP), fibrinogen, and C-fibronectin on admission and worse short-term outcomes. Elevated CRP, fibrinogen, and matrix metalloproteinases on admission are associated with poor functional outcomes and survival at 1–3 months.

Clinical Trials of IL-1Ra in Stroke
IL-1Ra has been evaluated in a single-center, phase 2 randomized controlled trial in patients presenting within 6 hours of acute stroke onset (85% ischemic; 15% ICH). The primary aim of this study was to evaluate safety and tolerability. Recombinant IL-1Ra or placebo was administered intravenously; 100 mg bolus, followed by 2 mg/kg per hour for 72 hours, and was well tolerated without significant safety concerns. All measures of clinical outcome were more favorable in the IL-1Ra–treated patients, although these were exploratory secondary analyses. In particular, there was a trend toward improved 3-month clinical outcomes (modified Rankin Scale and Barthel Index) in patients with cortical infarcts treated with IL-1Ra. Neutrophil leucocytosis, plasma CRP, and IL-6 were all substantially reduced in the IL-1Ra–treated group during the 72-hour infusion, providing biological proof-of concept for blockade of IL-1–mediated pathways. In secondary analyses, the effects of IL-1Ra on ex vivo peripheral blood cytokine induction were evaluated. At 24 hours and days 5 to 7, cytokine induction remained suppressed in the placebo group, whereas in those treated with IL-1Ra, the suppression of this induction was reversed. This raises the possibility that IL-1Ra may also reverse innate immune suppression by blocking IL-1–induced pathways involved in augmenting hypothalamic-pituitary adrenal axis activity. Reversal of peripheral immune suppression by IL-1Ra might reduce susceptibility to infection in the acute phase of stroke, which could improve clinical outcomes.

IL-1Ra has also been evaluated in a phase 2, double-blind, randomized controlled trial in patients with SAH requiring external ventricular drainage. This follows pharmacokinetic studies of IL-1Ra in similar cohorts where rapid and sustained CSF levels of IL-1Ra were observed, as seen in preclinical models also. The primary aim was to determine the effect of intravenous IL-1Ra on the concentration of inflammatory mediators in plasma and CSF. Patients were randomized to recombinant IL-1Ra (given as an intravenous bolus of 500 mg administered >1 minute, followed by a 24-hour infusion of 10 mg/kg per hour) or placebo. CSF and plasma were sampled serially (6, 12, 24, 36, 48, and 72 hours) for measurements of inflammatory markers. IL-1Ra reduced the concentration of IL-6 in CSF and plasma to the magnitude predicted; however, the numbers of participants recruited to the study was insufficient to achieve statistical significance (target of 32 patients, recruited 13, 6 of whom received IL-1Ra). Nevertheless, this study provides evidence that peripherally administered IL-1Ra has an effect in the central nervous system after SAH and may attenuate the inflammatory response after SAH possibly reducing the development of delayed cerebral ischemia.

As the intravenous formulation of IL-1Ra is no longer manufactured, UK phase 2 randomized controlled trials are investigating the effects of subcutaneous IL-1Ra in acute ischemic stroke (100 mg BID for 72 hours; ISRCTN74236229) or SAH (100 mg BID for ≤21 days; ISRCTN25048895). In the subcutaneous IL-1Ra in STROKE study, patients may receive thrombolysis if clinically indicated; the primary outcome measure is IL-6 between baseline and day 3; secondary outcomes include other peripheral inflammatory markers (CRP, leukocyte count, and von-Willebrand factor) and 3-month clinical outcomes (modified Rankin Scale, survival, and length of stay). The subcutaneous IL-1Ra in SAH study recruited 136 patients with aneurysmal SAH within 72 hours of ictus at 2 neurosurgical centers in the UK and has recently completed follow-up. Participants were randomized to IL-1Ra, administered as twice-daily subcutaneous injections for a maximum of 21 days after ictus, or until discharge from the study center, or no study treatment. The primary outcome measure is the effect of IL-1Ra on plasma IL-6 and CRP levels. Safety data were obtained throughout the inpatient admission and at 30 days via telephone and 6-month outcome recorded via telephone Glasgow Outcome Scale as a secondary outcome. Summary details of trials of IL-1Ra described are provided in Table 1.

Summary
IL-1Ra is a promising treatment for both ischemic and hemorrhagic stroke. There are extensive preclinical data in diverse models of cerebral ischemia, including aged and comorbid animals, and a recent cross-laboratory validation study. IL-1Ra is safe and well tolerated in patients with ischemic or hemorrhagic stroke and reduces inflammatory markers associated with worse outcome. However, on a cautionary note, it should be noted that many promising treatments for stroke have been in a similar position to IL-1Ra over the years and have failed to successfully translate to the clinic. Reasons for these failures and the predictive ability of stroke models have been discussed in many articles, as have suggested improvements for future research that might improve translation. In respect of these previous experiences, it is important therefore to highlight gaps in current knowledge relating to inhibition of IL-1 in stroke. There remains limited data on the therapeutic window for IL-1 inhibition, although one recent study reports efficacy of IL-1Ra up to 12 hours after intravenous treatment in rat MCAO. IL-1 exerts several biological effects that could improve functional recovery, including the release of growth factors, cell proliferation, and angiogenesis. Therefore, it is important to determine whether there is a limited window of opportunity to inhibit IL-1 poststroke and that if this is exceeded detrimental consequences might ensue. To our knowledge there are no studies investigating this, for example, by blocking IL-1 at extended time points after stroke onset. There are also no studies testing protective effects of IL-1 inhibition in larger species and limited data on long-term functional outcomes. Also, there is a need for more studies using thromboembolic models of stroke where reperfusion is obtained via tissue-type plasminogen activator to mimic the clinical
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AE indicates adverse events; AIS, acute ischemic stroke; aSAH, aneurysmal subarachnoid hemorrhage; BI, Barthel index; CRP, C-reactive protein; CSF, cerebrospinal fluid; DCI, delayed cerebral ischemia; ESR, erythrocyte sedimentation rate; EVD, external ventricular drain; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale; ICH, intracerebral hemorrhage; IV, intravenous; LOS, length of stay; MCP, monocyte chemoattractant protein; MRC, Medical Research Council; mRS, modified Rankin Scale; NIHR, National Institute for Health Research; NIHSS, National Institutes of Health Stroke Scale; RCT, randomized controlled trial; IL-6, interleukin-6; IL-1Ra, interleukin-1 receptor antagonist; SAEs, serious adverse events; SC, subcutaneous; TNF, tumor necrosis factor; vWF, von-Willebrand Factor; and WBC, White blood cell.
situation. Finally, IL-1Ra is a large protein with restricted brain penetration and relatively rapid elimination from the body. Although such features may actually be advantageous if acute inhibition of IL-1 in the periphery is what is optimal in treating stroke, there is a need for research on alternative approaches to block IL-1 such as caspase-1 inhibitors, antibodies, and small molecules. Finally, there are no studies investigating the effects of IL-1Ra in combination with other agents, either novel putative stroke treatments or existing medications that many patients with stroke will be taking, such as antiplatelets, antihypertensives, and statins.

As to the future, a phase 2 study investigating the effects of IL-1Ra on perihematomal edema in ICH is funded and will commence in 2018, after initial studies investigating the time course of IL-1 within the hematoma of patients participating in the MISTIE (Minimally Invasive Surgery Plus rTPA for ICH Evacuation) III trial (ISRCTN 81927110; UKCRN ID:20062) and the extent and colocalization of blood–brain barrier permeability and perihematomal microglial activation in patients with acute ICH (UKCRN ID:19650). In addition, a phase 3 multicenter efficacy trial is planned in SAH.

Further considerations before phase 3 testing in ischemic stroke include intra-arterial versus peripheral route of administration in patients receiving thrombectomy, patient selection, sample size considerations, and choice of outcomes. Finally, in view of its development in ischemic and hemorrhagic stroke, IL-1Ra could also be a candidate treatment for the prehospital paramedic setting, before brain imaging.

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