Subject: Interleukin-1 receptor antagonist penetrates human brain at experimentally therapeutic concentrations.

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The proinflammatory cytokine interleukin (IL)-1 mediates several forms of experimentally induced acute brain injury and has been implicated in chronic neurodegenerative disorders. The IL-1 receptor antagonist, IL-1RA, protects rodents against ischaemic brain injury, but its molecular mass (17 kDa) potentially limits the brain penetration of peripherally administered IL-1RA. We therefore sought to identify whether therapeutically effective concentrations of IL-1RA in the rat were also achieved in brain of patients with subarachnoid haemorrhage (SAH), using a peripheral administration regime that had proved to be safe and reduce peripheral inflammation in patients after stroke. An intravenous bolus of IL-1RA, followed by infusion, was administered to rats after induction of focal cerebral ischaemia. The effects of IL-1RA on brain ischaemia and the concentrations achieved in cerebrospinal fluid (CSF), were determined. Interleukin-1 receptor antagonist was similarly administered to patients with SAH, and CSF was sampled via external ventricular drains. In rats, IL-1RA significantly reduced brain injury induced by focal cerebral ischaemia. The plasma IL-1RA concentrations reached 12+/-2 microg/mL by 30 mins, and CSF concentrations were maintained between 91 and 232 ng/mL between 1 and 24 h of infusion. In patients with SAH, IL-1RA reached a steady-state plasma concentration of 22+/-4 microg/mL by 15 mins, and CSF concentrations were maintained at 78 to 558 ng/mL between 1 and 24 h. Intravenous delivery of IL-1RA leads to CSF concentrations in patients comparable to those that are neuroprotective in rats, and might therefore be of therapeutic benefit.