Herne Oxygenase-1 Induction in White Matter Following Intracerebral Hemorrhage

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Introduction:
Intracerebral hemorrhage (ICH) induces marked edema, demyelination and astrogliois in white matter. Recent findings demonstrate that clot-derived serum proteins can stimulate oxidative stress and induce white matter edema development and injury.

Rationale/Hypotheses:
Since induction of the heat shock gene, heme oxygenase-1 (HO-1; HSP32), is highly sensitive to oxidative stress, we tested the hypotheses that: 1) HO-1 expression is induced early in edematous white matter containing serum proteins after ICH, and, 2) the blood's plasma component alone can induce HO-1.

Methods:
We infused whole blood, plasma or packed red cells (2.5 ml) into frontal hemispheric white matter of pentobarbital-anesthetized pigs (11 kg) over 15 min. We monitored and controlled physiologic variables, froze brains in situ between 1 and 24 hrs post-ICH and sampled perilesional white matter. White matter from normal and sham animals served as controls. RT-PCR was performed on RNA extracts using standard methods and primers specific for porcine HO-1. Actin was the 'housekeeping' gene. HO proteins (inducible [HO-1] and constituitive [HO-2] isoforms) were determined by standard Western blotting and fluorsecence imaging.

Results:
HO-1 mRNA was rapidly induced in edematous white matter from whole blood-infused animals. Both blood components, i.e., plasma and red cells, similarly induced HO-1 message. HO-2 protein expression was unaltered by the infusate or time following ICH. HO-1 protein expression may be delayed since it was not detectable in the early hours.

Conclusions/Significance:
HO-1 gene expression is rapidly upregulated in white matter following ICH and can be induced by either the blood's red cell or plasma components. Although HO-1 protein expression appears not coincident with gene expression, this may be due to a weak sensitivity of the rat HO-1 antibody against the porcine protein. The ability of the blood's plasma component alone to induce an oxidative stress marker has implications not only for ICI-H, but also for pathophysiological processes with increased blood-brain-barrier permeability to plasma proteins.