Chapter 6

Src Family Kinases in Intracerebral Hemorrhage

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1. Introduction

Intracerebral hemorrhage (ICH), which accounts for 2 million (10–15%) of about 15 million strokes worldwide each year [1], has very high mortality rates of 31% at 7 days, 59% at 1 year, 82% at 10 years, and greater than 90% at 16 years [2,3]. ICH is associated with increased intracranial pressure, hematoma, blood brain barrier (BBB) disruption, brain edema, neuron loss, motor deficits, cognitive impairment and high mortality in humans. The major challenges immediately after ICH are re-bleed, hematoma induced brain injury, brain edema and neurological deficits [4]. Potential treatments of ICH include slowing the initial bleeding during the first hours after onset; removing blood from the parenchyma or ventricles to eliminate both mechanical and chemical factors that cause brain injury; management of complications of blood in the brain; and supportive medical care and surgery for certain patients [5]. Since these treatments have great variability, there is currently no FDA approved treatment for ICH.

The time course after ICH can be divided into two stages (acute/injury and chronic/recovery) (Fig. 1). At the acute stage, glutamine, thrombin, TNF-α, VEGF and other endogenous molecules are rapidly released following ICH. These molecules team up leading to brain cell death and severe brain injury via multiple neurotoxicity pathways, including (1) Excitatory amino acid (AA) and NMDA receptor-mediated excitatory toxicity; (2) Thrombin and other mitogen-mediated mitogenic stress; (3) Vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMPs)-mediated changes of vascular permeability; (4) Cytokines-mediated inflammatory responses; and others (Fig. 1).

As time course transits into chronic/recovery stage post-ICH, the elevated molecules resolve gradually and in turn participate in neurogenesis via populating neural progenitor cells (NPCs) to fix the damaged brain tissue. The possible mechanisms include (1) Excitatory amino acid (AA) and NMDA receptor-mediated excitatory genesis; (2) Thrombin and other mitogen-

mediated mitogenic growth; (3) Nerve growth factor (NGF), epidermal growth factor (EGF) and other growth factor-mediated neurogenesis; and others (Fig. 1).

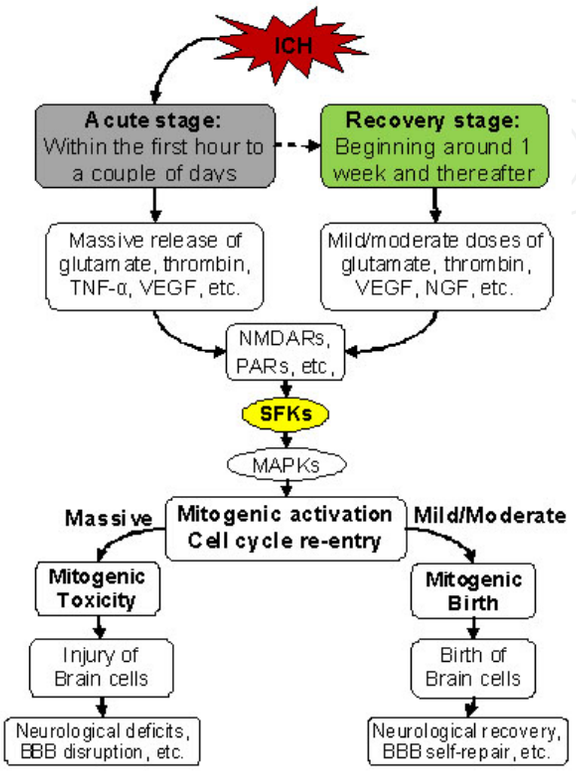

Figure 1. Src family kinases (SFKs) participate in mitogenic signaling pathways that play critical roles in blood-brain barrier (BBB) disruption and self-repair after intracerebral hemorrhage (ICH). The network does not apply to certain cell type(s). The arrows do not necessarily indicate direct binding and/or activation of the downstream molecules; intermediate proteins or kinases may exist.

Src family kinases (SFKs), a family of proto-oncogenic proteins, participate in both neurotoxicity at acute stage and neurogenesis during recovery stage post-ICH (Fig 1). Our previous studies have confirmed the time-specific and conflicting roles of SFKs using their inhibitor (PP2) after ICH: (1) Acute administration of PP2 (immediately post-ICH) decreases local cerebral glucose utilization (LCGU), activity of SFKs, attenuates BBB breakdown, brain edema, and cell death around ICH and improves behavioral function following ICH [6-9]; (2) Chronic inhibition of PP2 (2-6 days) blocks BBB repair and brain edema resolution in the recovery stage (7-14 days) after ICH [9].

2. Tissue specificity, structure and activity regulation of SFKs

SFKs are a family of non-receptor protein tyrosine kinases, include nine family members Src, Fyn, Lck, Lyn, Yes, Hck, Blk, Fgr, and Yrk [10-12], of which Src, Fyn, Yes and Yrk widely

expressed whereas the rest members are expressed in specific tissues [13]. In addition, one tissue can express multiple SFK members, for example, Src, Fyn, Yes, and Lck have been examined in brain [13-19]. Importantly, the different SFK family members often compensate for one another [20], which are supported by the evidence that the mice deficient in Src can survive though Src plays vital role in cell signaling transduction [20]. SFKs share a conserved domain structure consisting of consecutive SH3 (polyproline type II helix for protein-protein interaction), SH2 (phosphotyrosine recognition), and SH1 (tyrosine kinase catalytic activity) [12]. All SFK family members also contain an membrane-targeting region at their N-terminus that is followed by a unique domain of 50–70 residues, and the unique region is divergent among family members [12]. Although it still remains incompletely clear, Src activity is regulated by tyrosine phosphorylation at two sites (one is at Tyr416 in the SH1 domain, the other at Tyr527 in the short C-terminal tail), but with opposing effects. While phosphorylation at Tyr416 activates Src, phosphorylation at Tyr527 inactivates Src [13,21].

3. SFKs modulate NMDA receptor for brain injury after ICH

NMDA receptors are ionotropic glutamate receptors, comprise NR1, NR2 and NR3 subunits, which form the central conductance pathway [22,23]. In the physiological conductions, activation of NMDA receptors results in the opening of an ion channel that allows the flow of Na^+ and small amounts of Ca^{2+} into the cell and K^+ out of the cell [22,23]. Following ICH there is a transient increase of glutamate release and local cerebral glucose utilization in the region surrounding the ICH, and the antagonists of NMDA receptors reverse the glucose hypermetabolism produced by ICH [6]. However, glutamate alone could not explain the hypermetabolism since glutamate injected directly into brain did not produce hypermetabolism [6]. Apart from glutamate release, ICH may affect NMDA receptors in some way to make them more sensitive to glutamate in order to mediate injury and/or hypermetabolism.

ICH activates SFKs [7,8], and SFK members (e.g., Src, Fyn) up-regulate the ion channel activity of NMDA receptor and make them more sensitive to glutamate by phosphorylating the NR2A and NR2B subunits of the NMDA receptors [19,24-27]. It has been proved that phosphorylation by Src at Tyr-1292, Tyr-1325 and Tyr-1387 in NR2A subunit increases activity of NMDA receptors, and phosphorylation of tyrosine residues by Src in the C-terminal of the subunits prevents a Zn^{2+}-dependent inhibition of the NMDA receptors and thus increases channel conductivity [28-30]. We have demonstrated that either NMDA receptor inhibitors (MK-801) or SKF inhibitors (PP2) can attenuate brain injury at the acute stage after ICH (Fig. 2) [8]. These results suggest that either activation of NMDA receptors or SFKs is sufficient to produce brain injury post-ICH.

NMDA receptor activation has also been shown to enhance NPCs proliferation and lead to increased neurogenesis [31]. However, there is no direct report showing the mechanism by which SFKs participate in NMDA receptors mediated neurogenesis after brain injury.

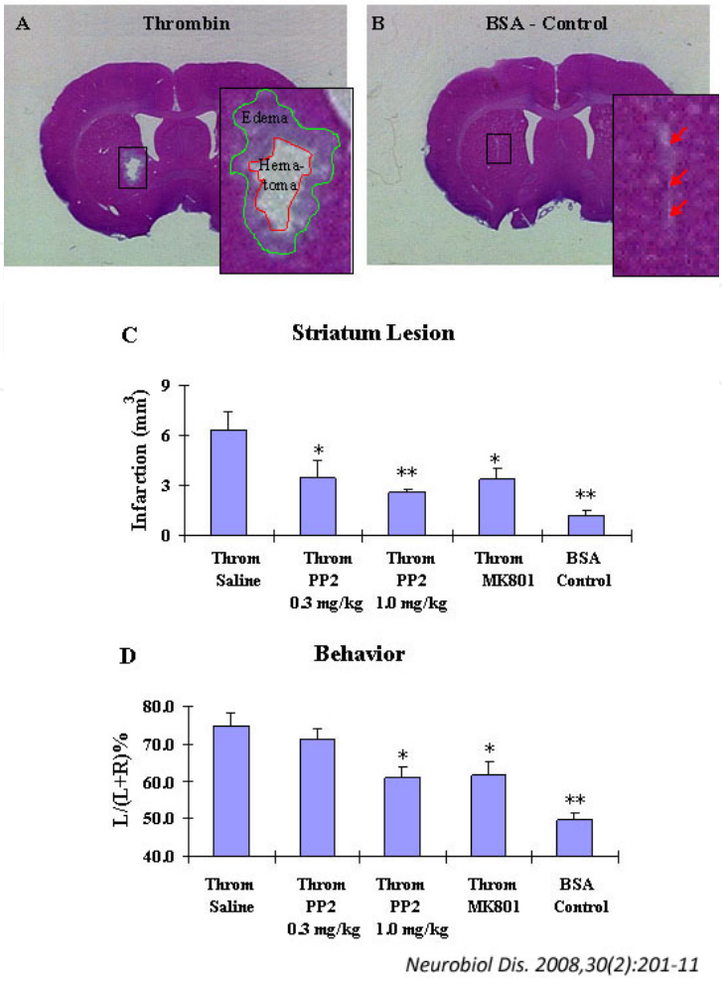

Figure 2. The effects of graded doses of SFK inhibitor PP2 (0.3 and 1.0 mg/kg, i.p.) and NMDA receptor inhibitor MK801 (1.0 mg/kg, i.p.) on injury produced by thrombin injections into striatum of Sprague-Dawley rats. **A.** Representative Hematoxylin-Eosin stained section shows that 20U of thrombin causes brain injury, including hematoma and edema. **B.** Control injections of BSA into striatum produced minor injury. **C.** Infarction volumes 24h following striatum injections of thrombin compared to control BSA injections (BSA/Control) (n=6). Several groups of animals received striatal injections of thrombin: just thrombin alone (Throm/Saline) (n=6); prior intraperitoneal injection of PP2 (Throm/PP2/0.3mg/kg) (n=6); prior intraperitoneal injection of a higher dose of PP2 (Throm/PP2/1.0mg/kg) (n=6); and prior intraperitoneal injection of MK801 (Throm/MK801/1.0mg/kg) (n=6).. * p<0.05 and ** P<0.01 vs Throm/Saline (one-way ANOVA followed by Dunnett's *post hoc* test). **D.** PP2 (0.3 and 1.0 mg/kg, i.p.) and MK801 (1.0 mg/kg, i.p.) decrease the thrombin-induced motor deficits (n=9 for each group) using Elevated Body Swing Test (EBST) 23.5 hours after thrombin injections. Biased swinging behavior was calculated as follows: L/ (L+R) (%) for left biased swings (L, left-biased swings; R, right-biased swings). * p<0.05 and ** P<0.01 vs Throm/Saline (one-way ANOVA followed by Dunnett's *post hoc* test).

4. SFKs regulate cell cycle for mitogenic toxicity and cell proliferation after ICH

The cell cycle is an irreversible, ordered set of events that normally leads to cellular division [32-36]. The release of cells from a quiescent state (G0) results in their entry into the first gap phase (G1), during which the cells prepare for DNA replication in the synthetic phase (S). This

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is followed by the second gap phase (G2) and mitosis phase (M). After the cell has split into its two daughter cells, the new cells enter either G1 or G0. Mature neurons normally maintain themselves in G0 resting phase; however, a mature neuron that re-enters the cell cycle can neither advance to a new G0 quiescent state nor revert to its earlier G0 state. This presents a critical dilemma to the neuron from which death may be an unavoidable, but necessary, outcome for adult neurons attempting to complete the cell cycle [32,37]. Increasing evidence have revealed that aberrant cell cycle re-entry leads to neuronal death [8,32,37-64], and cell cycle inhibition via blocking SFKs can protect neurons from death post-ICH [8].

Apart from post-mitotic neurons, SFKs play critical roles in the process of cell cycle in dividable cells, by regulating mitogen-activated protein kinases (MAPKs) and cell cycle proteins such as cyclin-dependent kinases (Cdks) [65-69]. Although mitogenic signaling is necessary to initiate the cell cycle for normal cell division and proliferation, massive mitogenic signaling can also produce neurotoxicity and cell death [9,32,37,70]. Cell death and cell proliferation seem contradictory to each other, but these two seemingly different cellular processes share some common mitogenic molecules and signaling pathways (Fig. 1). In addition, many other molecules, including Ca^{2+}, ROS, NO and MMPs can directly or indirectly activate or increase mitogenic signaling [54,71-77].

There are two stages (acute and recovery) after ICH (Fig. 1). Once ICH occurs, a large number of molecules (e.g., thrombin, glutamate, TNF-α, VEGF, etc.) are increased. This peaks within the first hour to a day in the acute stage after ICH, and then resolves gradually in the recovery stage after ICH. The over-activated SFKs/mitogenic signaling leads to neurons to enter the cell cycle and die, and damages astroctyes and BMVECs via MAPKs in acute stage after ICH. Within a day, however, the massive thrombin/SFK mitogenic signaling resolve, and the disease progresses to a recovery stage of ICH. The restored moderate SFK/mitogenic signaling leads to newborn BMVECs, astrocytes and other cells that mediate self-repair in the recovery stage after ICH.

As shown in Fig. 1, thrombin (a potent mitogen) triggers mitosis after ICH by modulating mitogenic intracellular molecules such as SFKs. SFKs participate in mitogenic signaling activation via regulating mitogen-activated protein kinases (MAPKs) and other molecules [64-69] that play critical roles not only in brain injuries during the acute stage in ICH, but in brain self-repair during the recovery stage in ICH. Acute inhibition of SFKs is beneficial, that attenuates hematoma, BBB breakdown, vasogenic edema, MAPK activation in the acute stage (0-24h) after ICH (Fig. 2, 3, 4, 5 & 6) [7-9,26,64,70]. In contrast, delayed and lasting inhibition of SFKs is detrimental, and prolongs BBB repair and brain edema resolution in the recovery stage (7-14 days) after ICH [9], presumably because SFKs mediate population of NPCs that exist in the "neurovascular niche". that repair the damaged BBB [78]. Such NPCs could serve as a source of newborn cells (i.e., BMVECs, astrocytes and perhaps other cells) of the neuro-vascular unit that play a role in re-establishing the BBB via the mitogenic growth signaling pathways during recovery phase after ICH (Fig. 1) [79].

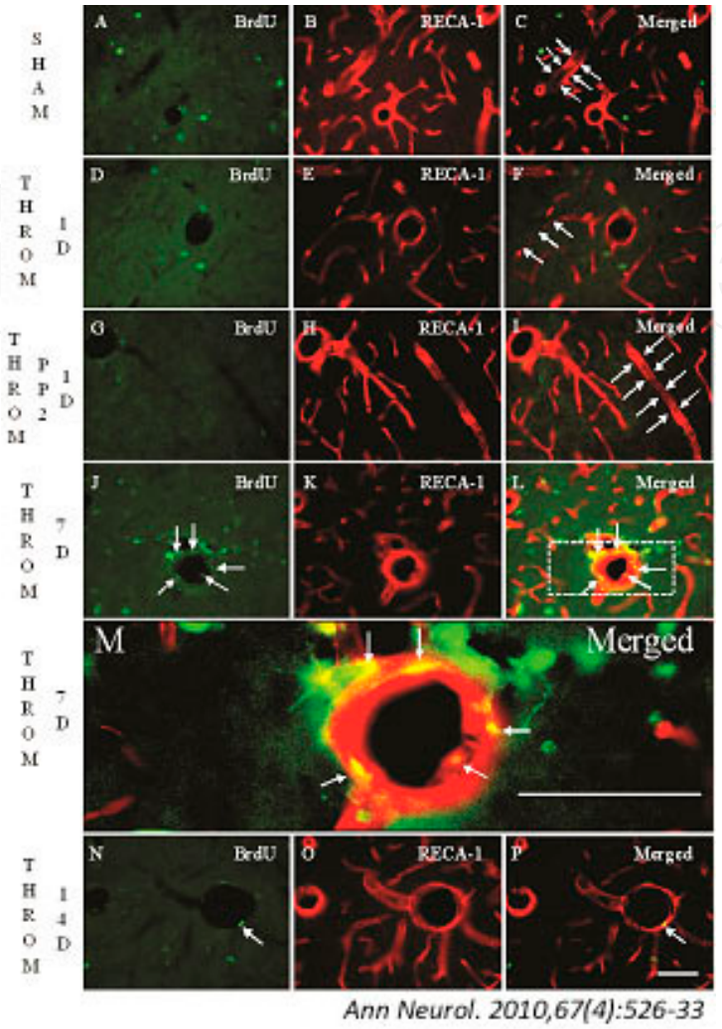

Figure 3. Intracerebroventricular (i.c.v.) injection of thrombin (20 U/animal, i.c.v.) causes reductions in brain microvascular endothelial cell (BMVEC) immunoreactivity after 1 day, and subsequent BMVEC proliferation around the brain vessels in lacunosum moleculare layer (LMol) of the hippocampus after 7 days and 14 days in Sprague-Dawley rats. **Panels A-C** show rats following sham operations labeled for BrdU, bromodeoxyuridine (A), RECA-1, rat endothelial antigen-1 (B) and the overlay or Merged image (C). RECA-1$^+$cells demonstrate the tube-shape of brain capillaries (arrows in panel C). **Panels D to F** show BrdU (D), RECA-1 (E) and the Merged image (F) at 1 day after thrombin injections. Compared with the sham group, RECA-1$^+$cells tend to lose their tube-shape at 1 day following thrombin injections (arrows in panel F) and there were no BrdU$^+$cells co-labeled with RECA-1 at one day (panel F). **Panels G-I** show the staining for BrdU (G), RECA-1 (H) and the Merged image (I) 1 day after thrombin plus PP2 injections. PP2 administration at day 0, immediately after thrombin injection, blocks the thrombin-induced loss of tube-shape of RECA-1$^+$cells. **Panels J-L** show the staining of BrdU (J), RECA-1 (K) and the Merged image (L) 7 days after thrombin injection. Compared to 1 day, BrdU$^+$cells are increased 7 days after thrombin injection. Some of these BrdU$^+$cells are co-labeled with RECA-1 (arrows in panel L and M). A few brain capillaries regained their tube-shape, though not completely. **Panel M** shows a higher power image of Panel L (area within dashed lines). RECA-1 stained BMVEC are red. The BrdU$^+$/RECA-1$^+$double-labeled new born BMVEC nuclei are yellow. **Panels N to P** show the staining for BrdU (M), RECA-1 (N) and the Merged image (P) 14 days after thrombin injection. Compared to 7 days, BrdU$^+$cells are decreased, but some BrdU$^+$cells (N) remain co-labeled with RECA-1 (arrow in panel P), and more and more brain capillaries regained the tube-shape 14 days after the thrombin injection. Scale bars: A-P, 50 μm.

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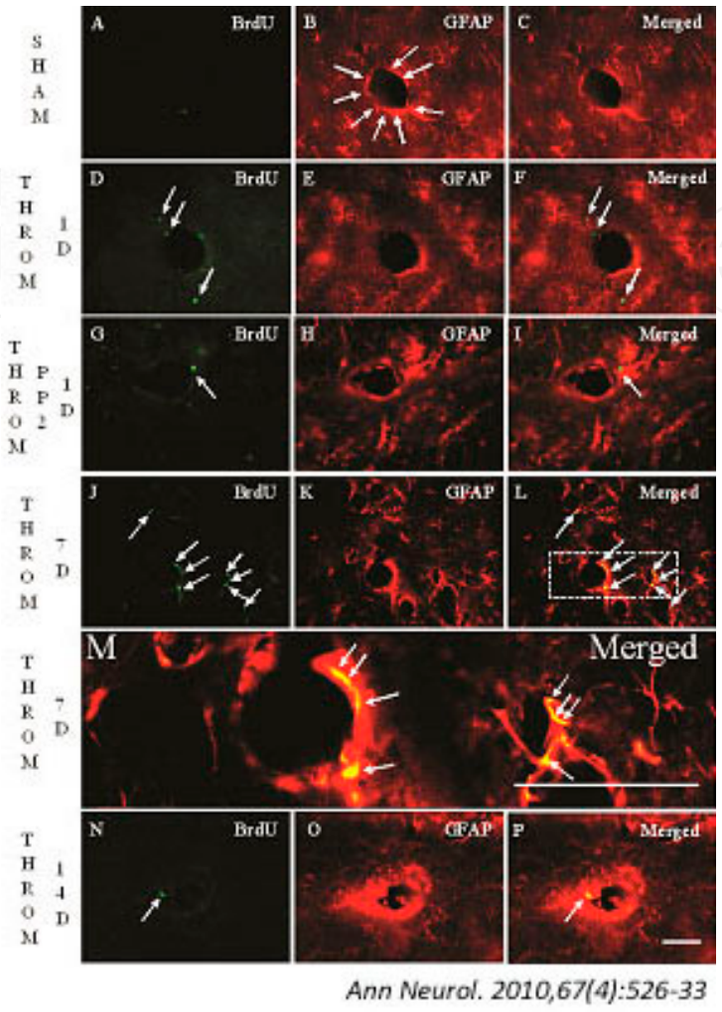

Figure 4. Intracerebroventricular injection of thrombin (20 U/animal, i.c.v.) causes reductions in astrocyte glial fibrillary acidic protein (GFAP) immunoreactivity after 1 day, and subsequent astrocyte proliferation around the brain vessels in lacunosum moleculare layer (LMol) of the hippocampus after 7 days and 14 days in Sprague-Dawley rats. **Panels A-C** show rats with sham operation labeled for BrdU (A), GFAP (B), and Merged image (C). $GFAP^+$cells envelop most all of the brain vessel (arrows in panel B). **Panels D-F** show BrdU (D), GFAP (E) and the Merged image (F) at 1 day after thrombin injection. Compared with the sham group, there is decreased GFAP immunoreactivity around brain vessels. There are a few $BrdU^+/GFAP^-$cells located close to the vessel (arrows in panel F). **Panels G-I** show the staining for BrdU (G), GFAP (H) and the Merged image (I) 1 day after thrombin plus PP2 injections. PP2 administration at day 0, immediately after thrombin injection, blocks the thrombin-induced reductions in GFAP immunoreactivity. **Panels J-L** show the staining for BrdU (J), GFAP (K) and the Merged image (L) 7 days after thrombin injection. Compared to 1 day, $BrdU^+$cells are increased 7 days after thrombin injection (J, arrows). Many of these $BrdU^+$cells are co-labeled with GFAP (arrows in panel L). **Panel M** shows a higher power image of Panel L (area within dashed lines). GFAP stained astrocytes are red. The $BrdU^+GFAP^+$double-labeled new born astrocytic nuclei are yellow (arrows, Panel M). **Panels N-P** show the staining for BrdU (N), GFAP (O) and the Merged image (P) 14 days after thrombin injection. Compared to 7 days, $BrdU^+$cells are decreased 14 days after thrombin injection. Some $BrdU^+$cells (N, arrow) remain co-labeled with GFAP (arrow in panel P) 14 days after the thrombin injection. Scale bars: A-P, 50 μm.

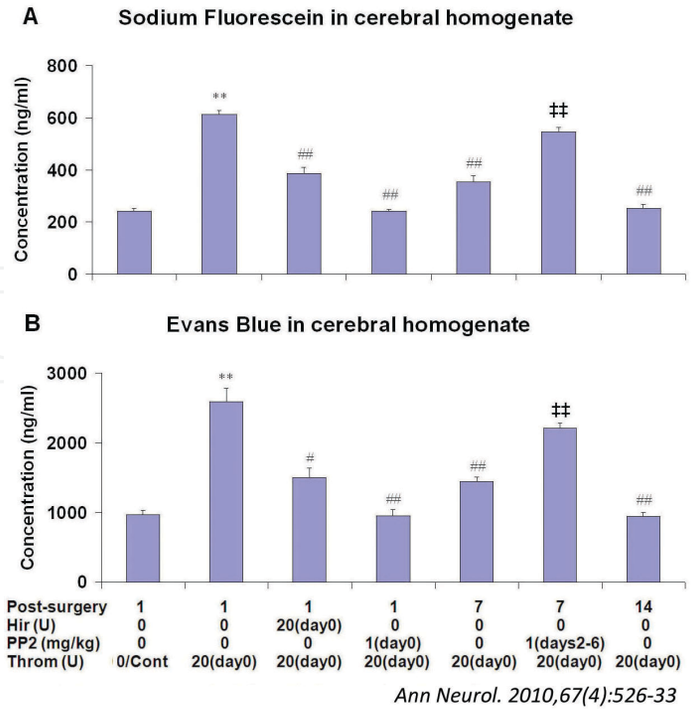

Figure 5. Brain sodium fluorescein (NF, **panel A**) and Evans blue (EB, **panel B**) extravasation increased 1 day after thrombin (Throm) injections (20U, i.c.v.), and decreased at 7 and 14 days in Sprague-Dawley rats. The thrombin inhibitor hirudin (Hir, 20U) blocked thrombin-induced NF/EB extravasation at 1 day after co-injection into the cerebral ventricles. PP2 (src family kinase inhibitor) administered with thrombin (day 0) blocked the NF/EB extravasation at 1 day after thrombin injection, whereas delayed PP2 administration (days 2-6) postponed alleviation of NF/EB extravasation at 7 days post-thrombin injection. Each column and vertical bar represents the mean ± standard error of the mean. ** p<0.01 vs. Cont; #p<0.05, ##p<0.01 vs. Throm/1day, ‡‡ p<0.01 vs. Throm/7days (one-way ANOVA followed by Tukey's *post hoc* test).

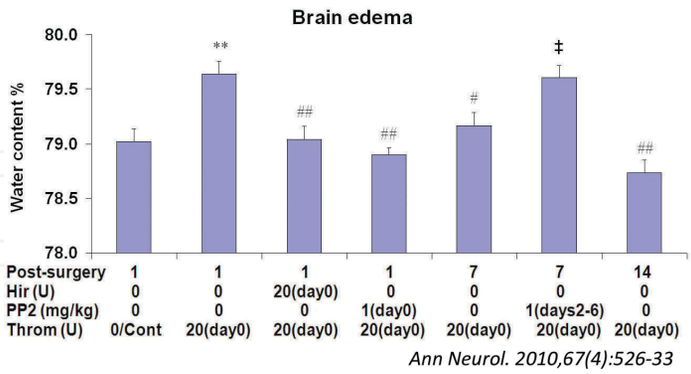

Figure 6. Brain edema (water content) increased at 1 day after thrombin (Throm) injections (20U, i.c.v.), and decreased by 7 and 14 days in Sprague-Dawley rats. The thrombin inhibitor hirudin (Hir, 20U, i.c.v.) blocked elevation thrombin-induced brain water content at 1 day after co-injection into the cerebral ventricle. Administration of PP2 (src family kinase inhibitor) at day 0 blocked the increase in brain water content observed at 1 day after thrombin injection, whereas delayed PP2 administration (days 2-6) prevented the resolution of brain water content at 7 days post-thrombin injection. Each column and vertical bar represents the mean ± standard error of the mean. ** p<0.01 vs. Cont; #p<0.05, ##p<0.01 vs. Throm/1day, ‡ p<0.05 vs. Throm/7days (one-way ANOVA followed by Tukey's *post hoc* test).

5. Future directions

Future studies need to address which specific SFK members found in brain (e.g., Src, Fyn, Lck and Yrk) that mediate ICH-induced cell death or birth. Since delayed and chronic inhibition of SFKs may impair neurogenesis and prolong BBB self-repair during recovery stage post-ICH, the acute and transient inhibition of SFKs should be pursued in treatment of ICH. The nanoparticle-based siRNA transfection system allows transient knockdown of target gene(s) and highly efficient delivery of siRNA *in vivo* with low cytotoxicity [80,81]. This could present a novel therapy for treating ICH patients as the nanoparticle-based siRNA approach provides heightened specificity for specific SFK gene(s) with less off target effects and this approach has been used in humans [82-85].

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