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Src Family Kinase Inhibitors and their Role in the Treatment of Traumatic Brain Injuries

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Abstract

Traumatic brain injury (TBI) leads to a broad spectrum of neurological deficits, including cognitive impairments that are irreversible and significantly influence quality of life even after recovery from physical disabilities. Clinically, there is no standardized procedure for treating secondary TBI, as each case is symptomatic. Src family kinase (SFK) inhibitors, a relatively new treatment regarding TBI, have so far been neuroprotective against secondary damage in non-human models. Immediately after TBI, there is increased expression of NR2A and NR2B. SFKs regulate NR2 subunits of NMDARs through tyrosine phosphorylation. Synthetic inhibitors of SFKs may help reduce the cognitive dysfunction seen after TBI by binding to SFKs and inhibiting the tyrosine phosphorylation of NMDARs, thereby preventing excitotoxicity within neurons that leads to cell death.

Keywords: Src family kinase; N-methyl-D-aspartate receptors; Traumatic brain injury; Injury; Edema; Oxidative stress; Ischemia; Hemorrhage; Thrombosis; Cerebral vascular dysfunction

Traumatic Brain Injury: Definition, Prognosis and Current Treatment Options

Traumatic brain injury (TBI) is a major medical concern in America, with greater than 50,000 deaths and 70,000-90,000 people suffering from disabilities annually. In the civilian population, TBI is caused most often by falls, and automobile or motorcycle accidents. It is the greatest cause of disability and death for people under 45 years old and is often seen in military personnel following head injuries in combat [**1**]. The incidence of TBI is growing in the military due to the extensive use of improvised explosive devices (IEDs) [**2**]. In fact, it is estimated that 15.2%-22.8% of returning military personnel from Iraq and Afghanistan were affected by mild traumatic brain injury (mTBI) [**3**]. These service members are among the 2.5-6.5 million individuals who undergo the agonizing socioeconomic costs associated with the long-term cognitive, physical and psychosocial deficits following TBI, totaling about 60 billion dollars annually [**4**,**5**]. Approximately 2% of the USA population lives with long-term disabilities due to a prior TBI [**6**]. TBI is also associated with long-term neurodegenerative diseases (e.g. Alzheimer's disease, Parkinson's disease, and Amyotrophic Lateral Sclerosis).

TBI in humans is often associated with cognitive dysfunction, the degree of which often depends on the injury severity. In the case of moderate to severe head injury in humans, the prognosis for recovery usually correlates with the level of post-traumatic trauma. Secondary brain damage is a common occurrence following the initial impact and is caused by edema, oxidative stress, ischemia, hemorrhage, thrombosis and/or cerebral vascular dysfunction [**7**]. These injures may be associated with marked anterograde amnesia (an inability to form and retain new memories) and retrograde amnesia (an inability to recall past memories) [**4**]. TBI leads to a broad spectrum of neurological deficits, including cognitive impairments that are irreversible and significantly influence quality of life even after recovery from physical disabilities [**8**]. An increasing amount of studies have looked at therapies for TBI, yet there is currently no accepted and effective treatment [**5**]. However, the expected method of treating patients would be by either protecting the brain from the negative effects of the primary or secondary damage, or delaying the secondary damage [**7**].

Clinically, there is no standardized procedure for treating secondary TBI, as each case is symptomatic. However, the primary treatment option is to reduce intracranial pressure (ICP) and minimize damage due to alterations in cerebral blood flow (CBF) and oxygen metabolism. The administration of osmodiuretics, such as Mannitol and hypertonic saline solution (HSS), reduce ICP by causing vasoconstriction. There are concerns with using Mannitol though, as it can cross the blood-brain barrier (BBB), accumulate in the brain, and cause a rebound effect, thereby increasing ICP [**9**]. HSSs are theoretically less likely to cross the BBB, making them an interesting alternative treatment for reducing ICP.

Multiple meta-analyses have shown that HSSs did not statistically significantly differ from Mannitol in reducing ICP following TBI. However, these meta-analyses are limited, as there are several differences noted between studies (dosage used, when neurological and mortality outcomes were assessed, HSS formulas, unblinded trials, etc.). Furthermore, a randomized controlled trial with sufficient power is needed to make definite conclusions about the use and effectiveness of each drug [**10**,**11**]. Another method of ICP reduction is decompressive craniectomy, where a portion of the skull is removed to expand the area around the swelling brain [**12**]. In one randomized controlled trial with 155 adults suffering from severe TBI, decompressive craniectomy was associated with decreased ICP

(p<0.001) and time spent in the intensive care unit (P<0.001). Unfortunately, this did not translate to improved scores on the Extended Glasgow Outcome Scale (odds ratio for an unfavorable outcome, 2.21; 95% CI, 1.14-4.26; P=0.02), a scale used to classify the mental state of TBI survivors [**13**].

To improve CBF, hypothermia, barbiturate coma, and hyperbaric oxygen therapy (HBOT) are used to decrease cerebral blood volume through vasoconstriction, decrease oxygen metabolism, and increase oxygen saturation to the brain [**12**,**14**]. While hypothermia has been shown to reduce intracranial hypertension, whether or not it has benefitted patients is unclear. In fact, in a study by Andrews et al. looking at 387 patients, hypothermia treatment did not result in better outcomes compared to standard care [**15**]. Not only that, but hypothermia might increase the risk of patients having cardiovascular complications or developing pneumonia [**16**].

Barbiturate coma therapy reduces cerebral blood flow, cerebral metabolism and ICP and may reduce mortality in a specific group of patients [**17**]. However, they have several concerning side-effects, such as hypotension, immunosuppression with a higher chance of infection, refractory hypokalemia, and potentially decreased white blood cell count [**9**,**18**,**19**]. HBOT is defined as providing 100% oxygen-enriched air to patients with a pressure greater than one atmosphere absolute. The efficiency of HBOT continues to be discussed, as standardized clinical studies examining the protective effects and exact benefit for TBI patients has yet to be conducted [**20**,**21**].

Regarding excitotoxicity, there is no pharmacological method currently accepted. Most clinical trials have looked at the effectiveness of NMDA antagonists. However, many trials were discontinued due to complications. Of the trials that were completed, essentially all of them were inconclusive or had an inadequate number of patients to determine the benefit or risk of their respective treatments [**22**]. Therefore, there is still a need for a secondary TBI option. Src family kinase (SFK) inhibitors, a relatively new treatment regarding TBI, have so far been neuroprotective against secondary damage in non-human models. One aspect of secondary damage that SFK inhibitors effectiveness have been particularly researched with is brain edema.

SFKs Mechanism of Action

The BBB is a tightly regulated interface that maintains brain volume and cerebral homeostasis to promote normal neuronal function. However, TBI disrupts normal functions through translational and rotational forces at the moment of impact (primary TBI), and brain edema (secondary TBI) [**23**]. Brain edema is defined as an increase in tissue volume due to excess accumulation of brain fluid content [**14**,**24**]. There are two major types of brain edema: 1. Cytotoxic, where extracellular water shifts into intracellular compartments of cells, and 2. Vasogenic, where the BBB is structurally and functionally impaired, allowing excess fluid (e.g. blood) to accumulate in the extracellular space in the parenchyma, causing an increase in ICP. It is currently thought that vasogenic edema most likely occurs during primary TBI, while cytotoxic edema occurs during secondary TBI [**25**]. Thrombin, a serine peptidase, is an essential clotting factor that contributes to brain edema and BBB damage following TBI. Multiple studies have shown that increased thrombin in the brain, either through a direct injection or TBI itself, mediates brain edema that can lead to neuronal death. Thrombin acts on protease activated receptors (PAR), which in-turn then activate protein kinases, such as src kinases [**26-28**].

Protein kinases are enzymes that transfer the terminal phosphoyl group of ATP onto a specific protein substrate, which is typically a tyrosine, threonine, or serine residue [**29**]. They mediate most signal transduction in eukaryotic cells and control many other cellular processes (cell cycle progression, metabolism, apoptosis, transcription, cytoskeletal rearrangement and cell movement, and differentiation) via this substrate modification. There are over 500 known protein kinases, with SFKs being of particular interest to researchers because of their role in various diseases [**30**,**31**]. SFKs consist of 11 non-receptor tyrosine kinases that include Src, Fyn, Yes, Blk, Yrk, Frk, Fgr, Hck, Lck, Srm, and Lyn [**31**,**32**].

SFKs have pleiotropic functions on mammalian cells, as they can affect cell morphology, metabolism, migration, invasion, proliferation, differentiation, and survival [**32**,**33**]. Within the central nervous system (CNS), SFKs are abundant in neurons [**34**]. Src has been shown to play a role in proliferation and differentiation during CNS development and is highly expressed in fully differentiated neurons. While it was originally thought that SFKs only had regulatory function in the CNS early in development, genetic ablation of SFKs in adult mice have caused several abnormalities, thus suggesting that SFKs may still have certain functions in post-mitotic neurons [**35**]. Another important function of SFKs in the developed CNS is to regulate the activity of ion channels, such as NMDARs [**35-37**].

NMDARs, subtypes of excitatory amino acid receptors, are implicated in multiple processes in the human brain. They play a role in mood and anxiety, attention and cognition, synaptic plasticity, CNS development, and even rhythm generation, which is necessary for functions like breathing and locomotion [**38**]. NMDARs are tetrameric ligand-gated cation channels that gate Na^+, Ca^{2+}, and K^+. They are composed of two NR1 and two NR2 (NR2A-NR2D) or two NR3 (NR2A and NR2B) subunits. The most common NMDAR channel conformation is a diheteromer of NR1/NR2A or NR1/NR2B, or as a triheteromer of N1/N2A/N2B (**39**). NMDARs are expressed in the prefrontal cortex, the hippocampus and in central association areas.'

When NMDARs are active, following postsynaptic membrane depolarization, they can induce long-term potentiation (LTP), which is a mechanism that contributes to the synaptic basis of memory formation [**39-41**]. The NMDA receptor antagonist AP5 has been shown impair Morris water maze (MWM) performance and block the induction of LTP in CA1 [**42**]. Furthermore, transgenic studies showed that knockout mice lacking the NR1 subunit of the NMDA receptor in CA1 were severely impaired in MWM performance [**43**]. Deregulation of NMDARs, as seen through excitotoxicity, can reduce LTP. NMDARs mediate excitotoxicity, which is the physiological mechanism that causes an increase of glutamate activity, opens calcium channels and then allows an excessive amount of calcium to enter. Large calcium concentrations due to intracellular store release and increased influx negates the regulatory functions within the cell, causing it to fail and potentially die [**44**].

SFKs regulate NR2 subunits of NMDARs through tyrosine phosphorylation, which has been found by physiological and pharmacological studies to be imperative for inducing LTP within the hippocampus [**34**,**44-46**]. For example, applying SFK-activating peptide (pYEEI) to cultured hippocampal slices causes an increase in NMDAR current, while Fyn-deficient mice undergoing the MWM task, a behavioral task that is considered to be hippocampal dependent, were impaired. Spatial learning is also associated with increased expression and activity of Src with NMDARs within the hippocampus [**37**].

However, over-activation of SFKs may lead to altered NMDAR expression that is detrimental to memory formation. It has been shown that immediately after TBI, there is increased expression of NR2A, NR2B, NR1, and GluR1 (an AMPA receptor subunit). The changes in NR2A and NR2B subunit expression are thought to be due to greater NR2B tyrosine phosphorylation and activation of extracellular signal-regulated kinases (ERKs) [**44**]. Therefore, synthetic inhibitors of SFKs may help reduce the cognitive dysfunction seen after TBI by binding to SFKs and inhibiting the tyrosine phosphorylation of NMDARs, thereby preventing excitotoxicity within neurons that leads to cell death. The pyrazolo-pyrimidinyl-amine compounds PP1 and PP2, SFK inhibitors, have been used extensively to study the cellular signaling mechanisms of SFKs [**47**]. Recently though, PP1 and PP2 have also been used in TBI models to determine their potential clinical utility.

SFK Inhibitor Treatment: Promising Results and Future Directions

SRC Family Kinase Inhibitors have been an overall effective method of treating TBI in non-human studies. For example, one study found that treatment with the SFK inhibitor PP2 immediately following LFP-induced TBI in rats decreased CA2/3 neuron loss and attenuated cognitive deficits at 16 days. Not only that, but PP2 also prevented the post-TBI upregulation of (ROCK1), a serine-threonine protein kinase implicated in tissue barrier dysfunction and hippocampal neuronal death following TBI [**28**,**48**]. Another study that treated TBI with PP2 found that it inhibited NR2B-phosphorylation and restored the subunits to their normal levels. Although PP2 was given immediately before TBI induction, it significantly improved neurological recovery from 7-10 days following TBI, suggesting that if given at the time that TBI occurs, it could potentially reduce certain aspects of secondary TBI [**44**].

In another study, pre-TBI treatment with the SFK inhibitor PP1 resulted in decreased breakdown of the blood brain barrier (BBB) due to inhibiting phosphorylation of ERK1/2. PP1 was also associated with decreased edema, increased levels of the tight junction protein zonula occludens-1 (ZO-1), and decreased levels of vascular endothelial growth factor (VEGF) [**49**,**50**]. These studies indicate that the timing of SFK inhibitor treatment in TBI is critical; SFK inhibitor therapy immediately after TBI can potentially ameliorate cognitive dysfunction. However, several studies have also shown that SFK inhibitors may have detrimental effects on cognition with prolonged use. For example, delayed PP2 administration given on days two through six post-TBI in one study extended BBB and brain edema disruption [**51**].

Even though there has been ample research supporting the beneficial role of SFK inhibitors in the treatment of TBI, there are still several questions that need to be addressed before it can be considered for clinical studies. One issue with current SFK inhibitors is that they interact with several different SFKs, so the exact mechanism in-which they improve TBI symptoms is not fully understood [**37**,**44**,**52**]. Furthermore, PP1 and PP2 are only preferential inhibitors of SFKs, meaning that they can also significantly inhibit other protein kinases [**47**]. Also, the specific SFKs that mediate tyrosine phosphorylation are unknown, even though Fyn kinase is a likely candidate [**44**,**52**]. Another aspect to consider is the other possible neurotoxins (e.g. glutamate, lactate, reactive oxygen species, hemoglobin) that are released into the CSF after TBI and how they might affect SFK expression and activity [**28**].

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