

● PERSPECTIVE

The kallikrein-kinin system: a promising therapeutic target for traumatic brain injury

Traumatic brain injury (TBI), which results from an outside force causing mechanical disruption of brain tissue, is potentially life-threatening and therefore a critical public health problem throughout the world. In the USA, approximately 1.7 million individuals per year sustain a TBI, and about 43% of patients hospitalized because of TBI develop long-term physical disability as well as psychological disorders, such as neurocognitive deficits, epilepsy, and depression (Roozenbeek et al., 2013). The primary brain damage that occurs due to the mechanical disruption of brain tissue is usually irreversible and therapeutically inaccessible. In the sequel, secondary injury processes, including blood-brain barrier disturbances, excitotoxicity with following generation of reactive oxygen species, and inflammation, contribute to the exacerbation of traumatic brain damage. One major predictor of outcome is the development of cerebral edema in the acute phase after brain injury. In addition to acute TBI, it has become evident over recent years that some TBI patients develop progressive brain atrophy and dementia, which is referred to as “chronic TBI”. It is speculated that in these “chronic TBI” conditions, neuroinflammation plays a decisive role. The treatment options for traumatic brain damage are limited and no specific drug therapy approved for TBI is available so far. Considering the highly relevant socio-economic burden of TBI, there is a pressing clinical demand for new therapeutic options. As the pathophysiology of TBI involves multiple mechanisms of secondary brain damage, successful therapeutic strategies must target its key pathological hallmarks. In this respect and according to current scientific evidence, drugs targeting the kallikrein-kinin system show promise in improving the outcome of TBI.

The kallikrein-kinin system as a promising therapeutic target: The kallikrein-kinin system mediates numerous pathophysiological effects, including vascular permeability, edema formation, inflammation, the release of excitatory amino acids (e.g., glutamate), and the production of reactive oxygen species (for a comprehensive review see Albert-Weissenberger et al., 2013). Kinins (e.g., bradykinin) are produced *via* two major pathways, one in the plasma and the other within the tissue. The cascade of kinin formation in the plasma is initiated by activation of coagulation factor XII (FXII, Hageman factor) after contact of plasma with negatively charged surfaces. Activated FXII converts prekallikrein to plasma kallikrein, while plasma kallikrein itself liberates bradykinin from kininogen *via* hydrolysis. The pathological effects of the kallikrein-kinin system are mediated by binding of bradykinin and other kinins to their respective receptors, *i.e.*, the B1 and B2 receptors. Interestingly, the plasma kallikrein-kinin system is linked to fibrinolysis, to the renin-angiotensin system, and to the intrinsic coagulation cascade. The kallikrein-kinin system and its components are implicated in multiple neuropathological states, including ischemic stroke, multiple sclerosis,

epilepsy, Alzheimer’s disease, and TBI, where neuroinflammatory processes contribute distinctly to disease severity (Naffah-Mazzacoratti et al., 2014).

Recent research on the impact of the kallikrein-kinin system on TBI: Over the past decades, accumulating evidence has suggested an important role of the kallikrein-kinin system in TBI (for a comprehensive review see Albert-Weissenberger et al., 2013). Generally, the B2 receptor is considered to have a major impact on different organs under pathological conditions. This paradigm, however, is changing as in recent years the reports on the roles of the B1 and B2 receptors in experimental TBI were inconsistent. Nikolaus Plesnila’s group subjected mice to controlled cortical impact that results in a predominantly focal brain damage (Trabold et al., 2010). They reported that in B2 receptor-deficient mouse brain, lesion size, brain edema, and functional impairment were diminished when compared with control mice (Trabold et al., 2010). In contrast, findings from Christoph Kleinschnitz’s group implicate that in murine focal brain trauma induced by cryolesion, B2 receptor deficiency has no significant impact on lesion formation or on the development of brain edema (Raslan et al., 2010). Moreover, B1 receptor-deficient mice were protected from acute focal brain trauma, as reflected by decreased brain lesions, brain edema formation, and inflammation in the injured brain area. These data were supported by pharmacological inhibition of the B1 receptor or the B2 receptor with R-715 and Hoe 140 administered 1 hour after induction of focal brain trauma, respectively (Raslan et al., 2010).

It is important to emphasize that human TBI is a heterogeneous disorder in which primary injury of brain tissue can be diffuse or focal, whereby the circumstances of the mechanical disruption of brain tissue govern the nature of the injury. Depending upon the nature of primary injury, various cell responses are triggered that can exacerbate the injury. Thus, the entire spectrum of events that might occur in TBI cannot be covered by one single model, and we therefore decided to analyze the impact of the kinin receptors on diffuse injury patterns as well. Our results show that, using a weight-drop model, B1 receptor-deficient mice, but not B2 receptor-deficient mice, are protected from diffuse brain trauma and showed less functional deficits when compared with control mice. Importantly, this protective effect was preserved at later stages of diffuse brain trauma (on days 3 and 7 after injury induction). Pharmacological inhibition of the B1 receptor with R-715 administered 1 hour after injury induction in wild-type mice had similar effects. As a possible underlying mechanism, we identified reduced axonal injury and astroglial activation that is associated with less neurodegeneration (Albert-Weissenberger et al., 2012). Considering that prior TBI increases the subsequent incidence of Alzheimer’s disease, it is interesting that growing evidence also suggests a pathophysiological role for the kallikrein-kinin system in Alzheimer’s disease (Viel and Buck, 2011). Similar to the situation in TBI research, studies on the distinct effects mediated by the B1 and B2 receptors in Alzheimer’s disease pathogenesis are partly inconsistent. After an intense literature research, Viel and Buck suggested a deleterious effect for the B1 receptor and a protective effect for the B2 receptor (Viel and Buck, 2011). Only recently, Lacoste and colleagues reported that B1 receptor protein is selectively upregulated



in activated astrocytes in a mouse model of Alzheimer's disease (Lacoste et al., 2013). Pharmacological B1 receptor inhibition with SSR240612 abrogates amyloidosis, and cerebrovascular and memory deficits in these mice (Lacoste et al., 2013). Moreover, the B1 receptor also could be involved in memory impairment and neurodegeneration as part of the normal aging process (Lemos et al., 2010). Collectively, these findings provide convincing evidence for a role of the B1 receptor in aging and Alzheimer's disease pathogenesis. Considering these research data, determining the long-term effect of pharmacological B1 receptor inhibition in the acute phase after TBI would be of particular importance.

Conflicting preclinical evaluations concerning the roles of the B1 and B2 receptors suggest caution when transferring observations made in animals into the human situation. Indeed, clinical trials using the B2 receptor antagonists Bradycor™ (deltibant, CP-0127) or Anatibant® (LF 16-0687) do not provide reliable evidence that kinin receptor B2 antagonists are effective in improving outcome after human TBI (Albert-Weissenberger et al., 2013). It is likely that inhibition of the kallikrein-kinin system at an earlier step of the cascade might be a more promising therapeutic strategy. Thus, we recently evaluated the impact of the C1-inhibitor, which acts on two different stages of the kallikrein-kinin cascade, as it is a serine protease inhibitor which effectively blocks activated FXII as well as plasma kallikrein. Our results prove that inhibition of the kallikrein-kinin system with the C1-inhibitor improves the outcome of mice subjected to cryolesion that results in focal brain trauma. Pharmacological treatment with 15.0 IU C1-inhibitor 1 hour after induction of focal brain trauma in mice resulted in decreased volumes of brain lesions after 1 day in both male and female mice. Importantly, this protective effect was preserved at later stages of focal brain trauma (days 3 and 5 after cryolesion). Our results implicate that the observed protection from focal brain trauma in C1-inhibitor-treated mice results from reduced blood-brain barrier damage and brain edema formation, diminished inflammation in the injured brain area, and less occurrence of thrombosis in the cerebral microvessels (Albert-Weissenberger et al., 2014).

To sum up, targeting the kallikrein-kinin system seems to be a successful therapeutic strategy to improve acute outcome and possibly even long-term recovery in TBI, as shown in several experimental set-ups. Despite inconsistent data on the effects of the B1 and B2 receptors, it is encouraging that all the preclinical studies show a detrimental impact of the kallikrein-kinin system on secondary brain injury. Considering the pathophysiological heterogeneity of TBI, the finding that the kallikrein-kinin system contributes to the pathology of diffuse and focal brain injury is of particular importance. As the kallikrein-kinin system enhances axonal injury, astroglial activation, and neurodegeneration in diffuse TBI, it seems to be highly probable that the inhibition of this system also improves the long-term consequences of TBI, such as the development of progressive brain atrophy and dementia. An attractive candidate for future clinical research to combat TBI is the C1-inhibitor, which inhibits the early steps of the

kallikrein-kinin cascade. However, investigations on long-term outcome weeks to months after injury are still missing and should be performed to avoid failures in translating the very promising preclinical findings to the clinic. As younger adults may be more resilient to the effects of TBI including the risk to develop dementia than older adults, also age-specific effects should be investigated.

This work was supported by the Else Kröner-Fresenius Foundation, Germany.

Sarah Hopp, Christiane Albert-Weissenberger*

Department of Neurology, University Hospital Würzburg, Würzburg, Germany

*Correspondence to: Christiane Albert-Weissenberger, Ph.D., albert_c2@ukw.de.

Accepted: 2015-04-18

doi:10.4103/1673-5374.158339 <http://www.nrronline.org/>
Hopp S, Albert-Weissenberger C (2015) The kallikrein-kinin system: a promising therapeutic target for traumatic brain injury. *Neural Regen Res* 10(6):885-886.

References

- Albert-Weissenberger C, Stetter C, Meuth SG, Göbel K, Bader M, Sirén AL, Kleinschnitz C (2012) Blocking of bradykinin receptor B1 protects from focal closed head injury in mice by reducing axonal damage and astroglia activation. *J Cereb Blood Flow Metab* 32:1747-1756.
- Albert-Weissenberger C, Mencl S, Schuhmann MK, Salur I, Göb E, Langhauser F, Hopp S, Hennig N, Meuth SG, Nolte MW, Sirén AL, Kleinschnitz C (2014) C1-Inhibitor protects from focal brain trauma in a cortical cryolesion mice model by reducing thrombo-inflammation. *Front Cell Neurosci* 8:269.
- Albert-Weissenberger C, Sirén AL, Kleinschnitz C (2013) Ischemic stroke and traumatic brain injury: the role of the kallikrein-kinin system. *Prog Neurobiol* 101-102:65-82.
- Lacoste B, Tong XK, Lahjouji K, Couture R, Hamel E (2013) Cognitive and cerebrovascular improvements following kinin B1 receptor blockade in Alzheimer's disease mice. *J Neuroinflammation* 10:57.
- Lemos MT, Amaral FA, Dong KE, Bittencourt MF, Caetano AL, Pesquero JB, Viel TA, Buck HS (2010) Role of kinin B1 and B2 receptors in memory consolidation during the aging process of mice. *Neuropeptides* 44:163-168.
- Naffah-Mazzacoratti Mda G, Gouveia TL, Simoes PS, Perosa SR (2014) What have we learned about the kallikrein-kinin and renin-angiotensin systems in neurological disorders? *World J Biol Chem* 5:130-140.
- Raslan F, Schwarz T, Meuth SG, Austinat M, Bader M, Renné T, Roosen K, Stoll G, Sirén AL, Kleinschnitz C (2010) Inhibition of bradykinin receptor B1 protects mice from focal brain injury by reducing blood-brain barrier leakage and inflammation. *J Cereb Blood Flow Metab* 30:1477-1486.
- Rozenbeek B, Maas AI, Menon DK (2013) Changing patterns in the epidemiology of traumatic brain injury. *Nat Rev Neurol* 9:231-236.
- Trabold R, Eros C, Zweckberger K, Relton J, Beck H, Nussberger J, Müller-Esterl W, Bader M, Whalley E, Plesnila N (2010) The role of bradykinin B(1) and B(2) receptors for secondary brain damage after traumatic brain injury in mice. *J Cereb Blood Flow Metab* 30:130-139.
- Viel TA, Buck HS (2011) Kallikrein-kinin system mediated inflammation in Alzheimer's disease in vivo. *Curr Alzheimer Res* 8:59-66.