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Ischemic stroke and traumatic brain injury: The role of the kallikrein–kinin system

Christiane Albert-Weißenberger [a], Anna-Leena Sirén [b], Christoph Kleinschnitz [a,*]

[a] University Clinic of Würzburg, Department of Neurology, Josef-Schneider-Str. 11, 97080 Würzburg, Germany
[b] University Clinic of Würzburg, Department of Neurosurgery, Josef-Schneider-Str. 11, 97080 Würzburg, Germany

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ABSTRACT

Acute ischemic stroke and traumatic brain injury are a major cause of mortality and morbidity. Due to the paucity of therapies, there is a pressing clinical demand for new treatment options. Successful therapeutic strategies for these conditions must target multiple pathophysiological mechanisms occurring at different stages of brain injury. In this respect, the kallikrein–kinin system is an ideal target linking key pathological hallmarks of ischemic and traumatic brain damage such as edema formation, inflammation, and thrombosis. In particular, the kinin receptors, plasma kallikrein, and coagulation factor XIIa are highly attractive candidates for pharmacological development, as kinin receptor antagonists or inhibitors of plasma kallikrein and coagulation factor XIIa are neuroprotective in animal models of stroke and traumatic brain injury. Nevertheless, conflicting preclinical evaluation as well as limited and inconclusive data from clinical trials suggest caution when transferring observations made in animals into the human situation. This review summarizes current evidence on the pathological significance of the kallikrein–kinin system during ischemic and traumatic brain damage, with a particular focus on experimental data derived from animal models. Experimental findings are also compared with human data if available, and potential therapeutic implications are discussed.

Contents

Abbreviations: B1R, kinin receptor B1; B2R, kinin receptor B2; BBB, blood–brain barrier; eNOS, endothelial isoform of NOS; ERK, extracellular signal-regulated kinase; FXII, coagulation factor XII; FXIIa, coagulation factor XIIa; GPCR, G-protein-coupled receptor; IL, interleukin; iNOS, inducible isoform of NOS; KKS, kallikrein–kinin system; MAPK, mitogen-activated protein kinase; MMP-9, matrix metalloprotease-9; NF, nuclear factor; NO, nitrit oxide; NOS, nitrit oxide synthase; PKC, protein kinase C; ROS, reactive oxygen species; TBI, traumatic brain injury; TNF, tumor necrosis factor; MCAO, middle cerebral artery occlusion.

* Corresponding author. Tel.: +49 931 20123755; fax: +49 931 20123488.
E-mail addresses: Albert_C2@klinik.uni-wuerzburg.de (C. Albert-Weißenberger), Siren.A@nch.uni-wuerzburg.de (A.-L. Sirén), christoph.kleinschnitz@mail.uni-wuerzburg.de (C. Kleinschnitz).

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1. Introduction

Acute ischemic stroke and traumatic brain injury (TBI) are major causes of mortality and morbidity. Stroke is the main cause of permanent disability and the second-leading cause of death worldwide, with 5.5 million stroke-related deaths per annum (World Health Organization fact sheet number 310, www.who.int/mediacentre/factsheets/fs310/en/). The incidence of stroke is also projected to rise owing to the increase in human life expectancy (Elkins and Johnston, 2003). Accordingly, approximately 14 million additional strokes are expected in the United States within the next 18 years with an estimated direct stroke related costs in 2030 around 143 billion Dollars (Roger et al., 2012). In Germany alone 3.5 million new strokes within the next 20 years are estimated to raise the direct stroke-related healthcare costs to around €110 billion (Kolominsky-Rabas et al., 2006). These significant economic impacts contrast with the availability of only one proven therapy against acute ischemic stroke, the use of early thrombolysis. Despite tremendous research activity, more than 100 clinical trials in human stroke have failed (O'Collins et al., 2006).

While stroke mainly affects the elderly, TBI is often caused by traffic or sport accidents, and is the leading cause of death and disability in adolescent and young males (Tagliaferri et al., 2006). TBI constitutes approximately 20% of all traumas, and has a very high disease-associated spending ($60 billion in the United States in 2000). Further, treatment options for TBI are very limited (Faul et al., 2007; Steudel et al., 2005); at present, the only effective method to treat severe TBI is to prevent its occurrence. Although several phase-II clinical trials have shown favorable effects of therapeutic compounds (Narayan et al., 2002), unfortunately all the compounds have failed to clearly show efficacy in phase-III trials (Doppenberg et al., 2004).

Despite differences in the underlying etiology of these complex diseases (Bramlett and Dietrich, 2004; Dirnagl et al., 1999), the events initiated after acute ischemic or traumatic brain insult share common pathophysiologies. For example, both stroke and TBI cause 'acute' (minutes to hours) and 'delayed' (hours to days/weeks) injury cascades, although in reality these sequential pathogenic events should be considered as a continuum (Fig. 1). The earliest pathological events after stroke comprise breakdown of transcellular ion gradients due to reduced oxygen and energy supply (Meuth et al., 2009), cytotoxic edema, production of toxic free radicals (Kleinschnitz et al., 2010a), and progressive thrombus formation in the cerebral microvasculature resulting from endothelial dysfunction (Stoll et al., 2008) (Fig. 1). At this early stage, a dysfunctional 'neurovascular unit' and breakdown of the blood–brain barrier (BBB) causes vascular edema that can cause brain tissue injury by simple compression (Ayata and Ropper, 2002). Edema formation is accompanied by a strong local inflammatory response leading to increased expression of numerous proinflammatory mediators and immune cell infiltration (neutrophils, T cells, and macrophages) (Iadecola and Anrather, 2011; Kleinschnitz et al., 2010b). Presumably, the majority of these inflammatory reactions contribute to neuron damage and vascular dysfunction, although some beneficial effects have been described, particularly for tissue reorganization and repair. Similar pathophysiological pathways are induced during TBI. Later stages of infarct development and TBI are characterized by delayed neuronal apoptosis (Fig. 1). This complex pathophysiology underlying stroke and TBI likely contributes to the failure of promising experimental

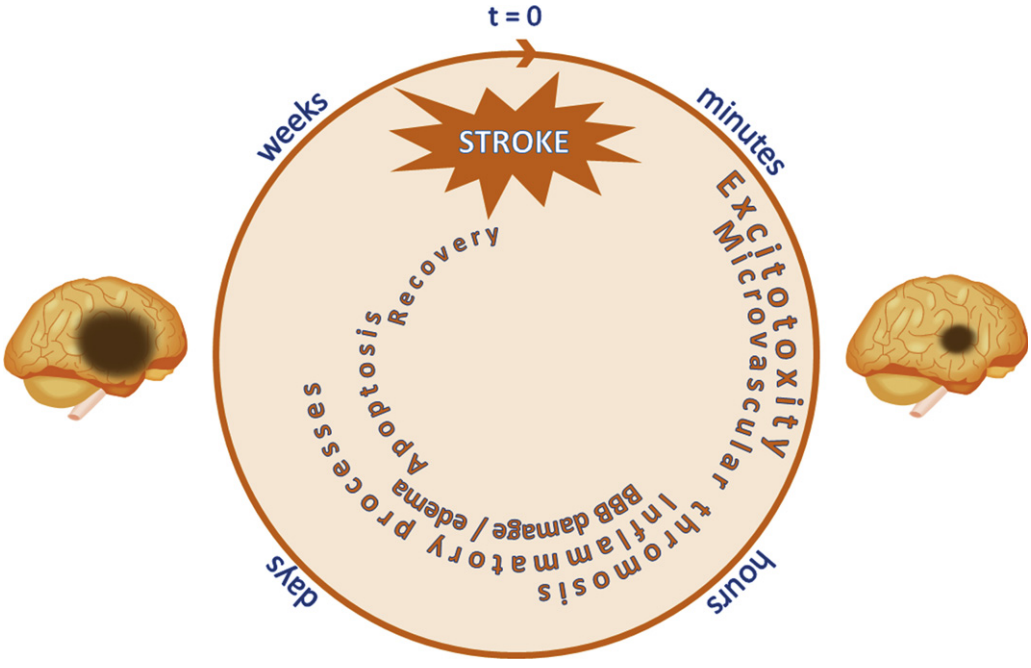

Fig. 1. Temporal sequence of the pathophysiological cascades in acute ischemic stroke. The size of the infarct core extends over time by evolution of the ischemic penumbra.