

Effect of Cerebral Glutamate on Epileptogenesis after Stroke

Abstract

One of the most significant causes of adult acquired epilepsy is stroke. Although cortical involvement and hemorrhage have been linked to an increased risk of seizures, the mechanisms behind the onset of epilepsy following a stroke remain a mystery. An excitotoxic effect of abnormal glutamate release following a stroke is one hypothesised mechanism. As a result of direct measurement of glutamate from the epileptic brain and analysis of receptors and transporters essential to glutamate homeostasis, numerous studies have implicated glutamate in the pathogenesis of seizures and epilepsy. Acute stroke is known to raise cerebral extracellular glutamate levels. There is little direct evidence linking the rise in glutamate during stroke with the later development of epilepsy, despite the fact that experimental evidence suggests that the cellular injury caused by glutamate exposure may result in the development of an epileptic phenotype. The lack of non-invasive methods for measuring cerebral glutamate has hampered clinical research in this area. Nonetheless, with the rising accessibility of 7T X-ray innovation, attractive reverberation spectroscopy is ready to more readily determine glutamate from other synthetic species at this field strength and Glutamate Substance Trade immersion move (GluCEST) imaging has been applied to confine epileptic foci in non-lesional central epilepsy.

Keywords: Hemorrhage Seizures • Epilepsy • Glutamate Homeostasis • Attractive reverberation spectroscopy

Introduction

According to Hauser, et al., one of the most significant causes of adult acquired epilepsy is stroke. Patients who suffer from epilepsy following a stroke have a higher risk of death and disability than patients who do not suffer seizures [1]. In addition, people who have suffered a stroke or transient ischaemic attack have worse long term functional outcomes with epilepsy.

The onset of epilepsy and seizures following stroke has been the subject of numerous studies. The reported incidence varies greatly from study to study; this is probably because there are different definitions, a wide range of patients with stroke or subarachnoid hemorrhage, and a lot of clinical variation [2]. In addition, the majority of studies include both early and late seizures, with various definitions of early seizures ranging from seizures occurring immediately following a stroke to those occurring two weeks later. In a cohort study of

our institution's patients with ischemic stroke, early onset and late onset seizures were found to occur in 10.1% and 5.8% of 138 non-rtPA treated patients, respectively, over the course of two years. A pooled analysis and systematic review of 102,008 patients demonstrated that people with haemorrhagic stroke or cortical involvement were more likely to experience post stroke seizures, with an overall incidence of 7%. There is evidence that venous sinus thrombosis and stroke both increase the risk of seizures.

Description

Risk factors for post stroke epilepsy

A multivariable prediction model for the onset of late seizures following ischaemic stroke was recently proposed by Galovic and colleagues based on five previously identified predictive factors for stroke severity, large artery atherosclerotic aetiology, early seizures, cortical involvement, and middle cerebral artery territory involvement [3]. Using this

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algorithm, it was determined that 83% of people at greatest risk would develop post stroke epilepsy within five years. Cortical involvement is one of several risk factors that has identified for the onset of post ischaemic stroke seizures a low Alberta Stroke Program Early CT Score (ASPECTS) score in 2016 and hemorrhagic transformation 2017. Additionally, we have demonstrated that the use of a code stroke system lowers the risk of epilepsy following a stroke.

The relationship between glutamate and stroke

In creature models, intense heights of glutamate levels have been seen after stroke, with those with the largest infarctions experiencing the highest elevations [4]. However, other studies have shown a decrease in glutamate levels, which is thought to be caused by a combination of decreased glutamate synthesis and the loss of brain glutamate through the cerebrospinal fluid and systemic circulation. Acute stroke has been associated with elevated intra cerebral glutamate levels as measured by cerebrospinal fluid in human studies, glutamate levels in the CSF and plasma were found to be correlated with the severity of neurological deficits and the infarction lesion. Although Src kinase activation and phosphorylation of glutamate receptors may play a different role in the pathogenesis of hemorrhagic stroke, glutamate elevation has also been linked to the pathogenesis of hemorrhagic stroke.

The glutamate and epilepsy

79 patients in the Yale epilepsy surgery program underwent microdialysis studies. When compared to non-epileptogenic cortex, the authors found elevated glutamate levels in epileptogenic, non-localized, and lesion cortical locations [5]. They also found that the epileptogenic hippocampus had higher levels of glutamate than the non-epileptogenic hippocampus. When compared to patients with histologically similar brain tumors without epilepsy, our group found elevated glutamate levels in the tumors and the surrounding peritumoural cortex in resected tissue [6].

The possibility of issues with the glutamate hypothesis

Experimental treatment with glutamate antagonists has failed to improve functional outcome, despite the strong evidence that glutamate related excitotoxicity is involved in the pathogenesis of stroke. However, the impact

on the onset of seizures was not investigated. Di Renzo, et al., go into great detail about the many possible causes of this failure [7,8]. Our understanding of post stroke epileptogenesis may benefit from some of these theories. In addition, in the event of an acute stroke, the neuro protective effect of extracellular acidity may outweigh the toxic effects of glutamate. However, it is possible that tissue acidosis prevents infarct growth but does not prevent the altered calcium homeostasis and cellular excitability seen in the structurally intact tissue [9]. It is likewise muddled if the harmful impacts of glutamate poisonousness are in any capacity counterbalanced by the simultaneous ascent in extracellular levels of the inhibitory synapse GABA [10].

Conclusion

One of the most significant causes of acquired epilepsy, especially in the adult population, is stroke. As a result, determining the cellular and molecular factors that contribute to the onset of post stroke epilepsy is a clinically urgent issue. In both animal and human studies, an increase in extracellular cerebral glutamate levels has been demonstrated following a stroke, particularly during the hyper acute phase. More recent magnetic resonance spectroscopy data suggests that glutamate may be part of a metabolic signature of hyper perfused tissue that is associated with relatively better clinical outcomes after reperfusion therapy. This is in contrast to the earlier findings that higher glutamate levels were linked to a worsening of infarct growth. Additionally, there is a lot of evidence to support the hypothesis that glutamate is involved in both the process of epileptogenesis and the initiation and propagation of seizure activity.

Acknowledgement

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Conflict of Interest

None.

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