

Our study suggests that local delivery of two trophic factors reduces neuronal damage and, specifically, may prevent the development of epilepsies that are caused by brain injury. Notably, the experiments were conducted under conditions that reproduce those that may allow therapeutic intervention in patients.

Epilepsies originating in the temporal lobe of the brain are the most common in adults. Pathological abnormalities can be observed in patients suffering these diseases. The most common is a loss of neurons in the hippocampus (a part of the temporal lobe) termed “hippocampal sclerosis”. These abnormalities develop in a previously healthy tissue: it is often identified an initial “epileptogenic” event [a head trauma, a stroke, a brain infection, or an episode of prolonged, uncontrolled seizures (status epilepticus)] that can produce damage and, after a latent period of weeks to years, is followed by the spontaneous occurrence of seizures, i.e. epilepsy. It can be hypothesized that embanking or repairing damage may lead to antiepileptic effects. This would represent a key advancement in therapy, because currently available anticonvulsant drugs do not prevent epileptogenesis and do not control seizures in about a third of the patients.

To date, however, the treatment of neurological diseases associated with neuronal death has been essentially restricted to attempts to prevent or limit damage. The discovery of neural stem cells disclosed the possibility of two new approaches: the transplantation of stem cells, or the recruitment of endogenous stem cells for generating new neurons by means of proliferation/differentiation factors. In view of the latter approach, key regulators of stem cell survival, proliferation and differentiation into neurons are proteins called “neurotrophic factors”. Endogenous neurotrophic factors are actually produced in the lesioned, epileptogenic tissue, but this process is evidently insufficient or inadequate for providing the endogenous stem cells with the proper cues to correctly proliferate, differentiate into neurons, and migrate in the correct position to restore function. Therefore, modulating the levels of neurotrophic factors in lesion areas may represent a new approach for the therapy of seizure-induced damage.

This study was designed to locally supplement specific neurotrophic factors within the hippocampus lesioned by prolonged seizures, in an attempt to suppress neuronal damage and to prevent the development of epilepsy. To pursue this aim, we generated a viral, herpes virus-based, vector. This vector was engineered to lose its pathological properties and, instead, to produce and supplement the tissue with the neurotrophic factors of interest. We chose to employ a combination of two neurotrophic factors, the fibroblast growth factor-2 (FGF-2) and the brain-derived neurotrophic factor (BDNF), because both protect neurons from ongoing damage and, further, FGF-2 is a potent proliferation factor for neural stem cells and BDNF appear to favor their differentiation into neurons.

We tested this viral vector in an animal model of neuronal loss, the hippocampal sclerosis induced by status epilepticus. In this model, an epileptogenic insult (an episode of prolonged seizures) causes a damage pattern in the hippocampus that closely mimicks the one observed in many epileptic patients. In time, animals begin to display spontaneously recurrent seizures, i.e. they become truly epileptic, again mimicking the situation observed in patients.

We injected the FGF-2 and BDNF-expressing vector in the hippocampus AFTER the establishment of hippocampal damage, that is, under conditions similar to those of a patient that, following occurrence of an epileptogenic insult, is in the latent period preceding the beginning of spontaneous seizures. The treatment allowed significant recovery from damage and significantly reduced spontaneous seizures after latency, that is, reduced development of epilepsy. These results are particularly striking considering that, at variance with the human disease, the animal model is accompanied by extensive damage also in extra-hippocampal regions, such that only a subset of spontaneous seizures originate in the hippocampus. In other words, seizures originating in the hippocampus are essentially abolished by treatment with the vector.

These data represent a conceptual advancement both in epileptology (concept: repair of damage prevents epileptogenesis) and in general (concept: it is possible to limit, or even to repair, damage by providing appropriate cues to the endogenous neural stem cells and progenitors – cues that are not available or insufficient in the injured tissue). These data may also have clinical ramifications, in that therapy was administered when damage was already in place, and may have a heuristic value for the many other neurological diseases associated with neuronal damage.