

Gene therapy involves the transfer and expression of a therapeutic gene into a target tissue and may provide a realistic therapeutic option for CNS disorders difficult to treat with conventional drugs. Gene therapy applied to the brain should take into special account the presence of the blood-brain barrier, the largely postmitotic and limited regenerative nature of neurons, the heterogeneity of cell types, and critical functions of specific neuronal circuits. The promising potential of gene therapy for applicability to human pathology still requires improvements of efficacy and safety. This innovative approach may represent a concrete possibility of therapeutic intervention for epilepsy, one of the most prevalent neurological disorder that affects about 1% of the population worldwide. Currently available anticonvulsant therapies do not control seizures in about a third of epileptic patients. In principle, patients with intractable seizures of focal onset may benefit from therapeutic strategies alternative to resective surgery, such as the delivery of molecules into the seizure focus with potential anticonvulsive and antiepileptogenic properties. Potentially interesting therapeutic gene candidates are the neuropeptides galanin and NPY, and neurotrophic factors (NTFs) given their wide distribution in areas of seizure onset and spread, their regulation by seizures and their ability to significantly attenuate seizures and the associated neuropathology *in vivo*. Adeno-associated viral vectors (AAV) carrying different expression cassettes have been engineered to appropriately traffic and release neuropeptides *in vivo*, providing either a constitutively secreted galanin or an activity-regulated NPY release from the transduced neurons. Importantly, *in vivo* infusion of neuropeptide-expressing vectors attenuated focal seizure activity and delayed kindling epileptogenesis. Additionally, galanin overexpression prevented kainic acid-induced hippocampal neuronal cell death. NTFs may also exert favorable effects on seizure-induced damage. Herpes simplex vectors have been used to locally supplement FGF-2 and BDNF in a lesioned hippocampus. NTFs expressing vectors increased neuronogenesis, repaired neuronal damage and prevented epileptogenesis. GDNF, a member of the transforming growth factor-beta superfamily, acts as a survival factor for dopaminergic and noradrenergic neurons, and spinal motoneurons. AAV-mediated GDNF overexpression in the hippocampus suppressed generalized seizures and kindling epileptogenesis. GDNF-producing encapsulated cells transplanted intrahippocampally also mediate a decrease in kindled seizure severity and duration. It is concluded that *in vivo* gene delivery of specific neuropeptides and NTFs in lesion areas may represent a new approach for the therapy of seizures and the associated neuropathology in human epilepsy.