CAN EPILEPSY AND ITS NATURAL HISTORY BE PREVENTED? – NO.

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'Treatment of epilepsy' is a commonly used term, though not entirely correct. The 'antiepileptic' drugs we are administering to patients with epilepsy aim to prevent the recurrence of unprovoked epileptic seizures, therefore, our approach is rather a secondary prophylaxis. For many reasons, it is a fascinating idea not only to suppress seizures in established epilepsy but to prevent the development of the disease. Epileptogenesis following acquired brain injuries such as cerebrovascular incidents, trauma, central nervous system infections or status epilepticus has been and still is the aim of much research interest, in particular regarding pathophysiological mechanisms. Following experimental status epilepticus, NMDA receptors regulated circuit modifications in the hippocampal formation resulting in a transient loss of inhibition and in an increased excitation are currently assumed to represent the pathophysiological basis for epileptogenesis. Morphological correlates are loss of hilar inhibitory interneurons and sprouting of dentate gyrus granule cell axons ('mossy fibers').

In experimental animals models, antiepileptogenic or disease-modifying pharmacostrategies following status epilepticus have been studied extensively, but so far experimental data on preventive approaches after other epileptogenic aetiologies such as traumatic brain injury or ischaemic stroke are lacking. As a number of relevant processes underlying epileptogenesis are believed to be NMDA receptor regulated, pharmacological blockade of these receptors seems to be a reasonable antiepileptogenic treatment approach.

In a model system of kainate induced SE, the administration of the NMDA receptor antagonist MK-801 immediately after termination of 90 min lasting seizure activity did not prevent or attenuate the development of chronic epilepsy. Model discrepancies may explain the conflicting results regarding the antiepileptogenic effect of valproate that completely prevented the development of epilepsy following kainite induced SE, while spontaneous seizures following electrically induced SE were not affected at all. Carbamazepine administered for 8 weeks starting 24 h after termination of pilocarpine-induced SE did not prevent the development of chronic epilepsy, however, spontaneous recurrent seizures occurred less frequently and duration was shorter compared to vehicle-treated control. This study demonstrates disease-modifying effects of carbamazepine that is one of the most common drugs with strong seizure preventing properties in patients with partial epilepsies. However, these findings by now have not been reproduced by other authors. Further substances tested in experimental animals such as lamotrigine, vigabatrin, phenobarbital, ketamine, and levetiracetam did not prove to exhibit any antiepileptogenic or disease-modifying properties.

In patients, antiepileptogenic pharmacostrategies methodologically can be assessed only when substances were administered for a defined period of time after a potentially epileptogenic event to prevent the occurrence of late unprovoked epileptic seizures at a time point when the drugs had already been withdrawn. Unfortunately, available clinical trials on carbamazepine, phenobarbital, phenytoin, and valproic acid so far did not reveal any satisfactory results. A Cochrane review incorporating six randomised controlled trials with more than 1,400 patients revealed that seizure-suppressing drugs administered after traumatic brain injury do not have any antiepileptogenic or disease-modifying effect regarding the development of chronic epilepsy.

In summary, up to now any substance assessed in experimental animals and in patients after acquired brain injuries was not convincingly capable to prevent the development of epilepsy. A better understanding of the pathophysiological mechanisms underlying epileptogenesis is the prerequisite for the development of new and sufficient antiepileptogenic treatment strategies.

The natural course of epilepsy is largely unknown as long term follow-up studies covering decades are difficult to perform and therefore rare. Idiopathic generalised epilepsies are assumed to exhibit less epileptogenicity when patients become older, and therefore, discussion of preventive strategies is gratuitous. In contrast, partial epilepsies, and in particular mesial temporal lobe epilepsy, are discussed to be progressive conditions, but available neuroimaging and neuropsychological data are conflicting. Gower's verdict that "seizures beget seizures" suggests a kindling phenomenon in epilepsy that may be true in experimental animals but has never been demonstrated in patients. Response to antiepileptic drug treatment is not different in patients after one or a few seizures compared to long lasting untreated epilepsy with hundreds of fits.

In summary, all these data give no hint that epilepsy itself has a progressive natural course unless the underlying aetiology such as neoplasms or neurodegenerative disorders is progressive. Preventive strategies are therefore not applicable.