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A role for inflammation in status epilepticus is revealed by a review of current therapeutic approaches

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Summary

A significant number of epileptic patients fail to respond to currently available anti-epileptic drugs. This suggests a need for alternative approaches to reduce the occurrence of seizures in these patients. Recent data have shown that in addition to well-known neuronal mechanism, seizures may be a consequence of misguided inflammatory response and blood-brain barrier disruption. Both peripheral and brain pro-inflammatory events have been demonstrated to govern the onset of status epilepticus. Evidence deriving from the experimental and clinical realms supports the notion that a role for pro-inflammatory and cerebrovascular events in seizure disorders is broader than previously suspected. As a result, methods to pharmacologically reduce blood-brain barrier permeability and reduce inflammation have thus emerged as means to reduce seizure burden. For instance, corticosteroids have been shown to be beneficial and the same agents may be able to further reduce seizure burden in conjunction with currently prescribed anti-epileptic drugs.

Keywords

Blood-Brain Barrier; anti-epileptic drugs; glucocorticosteroids; seizures

The current direction of epilepsy research has substantially changed from the conventional focus. In the past, the traditional approach based on a neurocentric view of seizure generation promoted understanding of the neuronal mechanisms of seizures. These efforts

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resulted in the development of potent anti-epileptic drugs (AEDs) and triggered refined surgical approaches to treat multiple drug resistant seizures. However, the fact that a significant number of epileptics still fail to respond to available AEDs restates the need for an alternative approach.

Two emerging players hold the lion's share of "unconventional" epilepsy research. On one hand, inflammation is becoming an essential topic linking the immune system to neuronal dysfunction. On the other, altered blood-brain barrier (BBB) permeability plays an important etiological role in seizure generation. The BBB has recently been targeted to develop new pharmacological approaches aimed at restoring homeostasis and normal function. Combination therapies utilizing an AED in conjunction with BBB-stabilizing corticosteroid therapy may control seizures better than AED therapy alone (Marchi et al., 2011b). Experimental and clinical evidences support the use of anti-inflammatory drugs to treat seizures; these results have been published and reviewed (*e.g.*, (Janigro 2012;Vezzani & Granata 2005)). This short article will use an indirect approach in an attempt to further the notion that seizures can be prevented or treated by targeting systemic inflammation and its gate keeper, the BBB. In particular, we will focus on SE and its management.

In *status epilepticus* the role of BBB-immune interactions is poorly understood but if one considers the therapeutic approaches to treat SE, a surprising overlap with anti-inflammatory maneuvers becomes apparent (Marchi et al., 2012;Shorvon & Ferlisi 2011). These therapeutic options span from drugs acting on GABA receptors (benzodiazepines, anesthetics and barbiturates), to anti-inflammatory drugs (corticosteroids) and to other maneuvers with direct or indirect, documented or unknown, mechanisms of action on neurons.

One extreme of the spectrum of treatments for SE are GABA-ergic drugs or anesthetics which quickly (<1 hr.) achieve the desired anti-SE effect. For these, a direct effect on neurons and modulation of inhibitory synapses is the unquestionable *modus operandi*. However, anesthetic drugs also have immunomodulatory effects partially overlapping with those of corticosteroids. For instance, propofol or thiopental exert potent anti-inflammatory effects mediated by decreased NF-κB expression (Roesslein et al., 2008;Sanchez-Conde et al., 2008). Sevoflurane, which has similar anesthetic potency but lacks anti-inflammatory action, is not the first choice among halogenated anesthetics for SE. Furthermore, sevoflurane may actually have an epileptogenic effect (Jaaskelainen et al., 2003). These anti-inflammatory mechanisms are comparable to what is observed with corticosteroids and aid in the prevention, or recovery of BBB integrity (Marchi et al., 2009a;Marchi et al., 2011a;Verhelst et al., 2005).

An emerging therapeutic approach to refractory SE (reviewed by (Shorvon & Ferlisi 2011) is the use of intravenous infusion of magnesium sulphate. Magnesium has negligible BBB permeability and, in healthy individuals, brain levels exceed serum concentrations (Amtorp & Sorensen 1974). When the BBB is disrupted (*e.g.*, during seizures), brain Mg^{++} may decrease due to brain-to-blood leakage. This causes a partial, seizure-promoting NMDA receptor disinhibition. Thus, systemic administration to achieve high magnesium levels in

blood may prevent leakage or restore brain levels of this ion, with a pronounced effect on excitatory synapses and thus on neuronal excitability.

Last but not least, traditional AEDs exert immunological effects. While an ample array of contradictory data exists, AEDs interfere with normal immunological responses leading to the activation of proinflammatory pathways that may lead to or exacerbate seizure activity (Beghi & Shorvon 2011).

There are several issues that need to be clarified before our understanding of inflammation and seizures translates into meaningful drug or therapeutic development. For example, it is not known if “fixing the barrier”, as with corticosteroids (Cucullo et al., 2004;Hoheisel et al., 1998), is sufficient to treat SE or other forms of seizures, or whether a full-blown anti-inflammatory action is necessary. It is our opinion that BBB repair alone may be sufficient in SE when the initiating trigger consists of a permeability change leading to acute neuronal synchronization (as for example after iatrogenic blood-brain barrier disruption (Marchi et al., 2007;Marchi et al., 2010a;Marchi et al., 2010b) or BBB loss by non-iatrogenic means (Ivens et al., 2007). When the cascade of events leading to seizures is more complex, as in encephalopathies or other panencephalic disease forms, it is likely that a broader anti-inflammatory action is needed, perhaps consisting of use if more than one therapeutic modality (e.g., steroids and hypothermia or magnesium supplementation). An impediment to the development of these new combination therapies is the lack of recognized animal models. Pilocarpine has gained ground on systemic/ intraparenchymal kainic acid, or electrical kindling as a model of TLE; given the involvement of the brain-inflammatory axis in this model, we suggest that the pilocarpine model, or its variant Li-pilocarpine (Marchi et al., 2009b), should be used as a paradigm for exploratory studies on SE treatments based on anti-inflammatory agents. In the case of acute, provoked seizures, osmotic blood-brain barrier disruption with intrarterial mannitol has the advantage of being readily available in many species, and the undisputed advantage of having been tested in human subjects.

In addition, BBB repair may lead to a beneficial “pharmacokinetic” effect. Several AED are, in blood, bound to serum proteins; the AED-protein complex does not permeate across the BBB and only the dissociated, “free” AED creates the gradient for concentration-driven accumulation into the brain. In the case of BBBD, this equilibrium is perturbed, resulting in the accumulation of AED and plasma proteins into the brain, altering the level of interstitial free AED. Re-establishing a proper blood-to-brain separation could counterbalance this phenomenon. “Fixing” the BBB could have a two-pronged effect; it would reestablish the proper brain interstitial ionic homeostasis (Janigro, et. al, 2012) and allow for AED passage across the BBB according to the drug chemical and physical proprieties (*e.g.*, molecular weight, lipophilicity, etc.). The latter hypothesis further supports therapeutic approaches where an AED and a cerebrovascular / anti-inflammatory drug are concomitantly administered.

In conclusion, these are exciting times for the epilepsy research community, with many new approaches, forms of disease and disease models being developed (see for example (Fabene et al., 2008;Ivens et al., 2007;Maroso et al., 2009;Nabbout et al., 2011;van Vliet et al.,

2007) . A combined approach including neurologists, neuroscientists and immunologists will likely leapfrog the field of treatment of SE and perhaps other epilepsies.

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