LETTER TO THE EDITOR

The blood–brain barrier hypothesis in drug resistant epilepsy

Nicola Marchi,1,2 Tiziana Granata,3 Andreas Alexopoulos4 and Damir Janigro1,2,5,6

1 Molecular Medicine, Cleveland Clinic Foundation, Cleveland, OH 44195, USA
2 Cell Biology, Cleveland Clinic Foundation, Cleveland, OH 44195, USA
3 Istituto Neurologico Besta, 20133 Milan, Italy
4 Epilepsy Center, Cleveland Clinic Foundation, Cleveland, OH 44195, USA
5 Neurological Surgery, Cleveland Clinic Foundation, Cleveland, OH 44195, USA
6 Cerebrovascular Research, Cleveland Clinic Foundation, Cleveland, OH 44195, USA

Correspondence to: Nicola Marchi,
Cleveland Clinic – Molecular Medicine and Cell Biology,
9500 Euclid Ave Cleveland Ohio 44195, USA
E-mail: marchin@ccf.org

Sir, We read with great interest this succinct, informative and focused update on the therapeutic approach to super-refractory status epilepticus (SRSE) by Shorvon and Ferlisi (2011). In particular, we were pleased to see the ‘blood–brain barrier failure’ displayed as a potential seizurogenic mechanism. The authors provide a comprehensive update on the treatment options, and a thoughtful rationale for the timing of interventions. We noted that the authors present in Fig. 1 and Table 1 a number of anti-SRSE choices spanning from drugs acting on γ-aminobutyric acid (GABA) receptors (benzodiazepines, anaesthetics and barbiturates) to anti-inflammatory drugs (corticosteroids) or to other treatments with direct or indirect, documented or unknown, mechanisms of action on neurons.

It is reasonable to assume that if and when GABA-ergic drugs or anaesthetics quickly (<1 h) achieve the desired anti-status epilepticus effect, then their action is consistent with the modulation of inhibitory synapses. However, anaesthetic drugs also have immunomodulatory effects partially overlapping with those of corticosteroids. These effects may become of therapeutic value only when an immediate short-term, GABA-mediated effect is unachievable (e.g. Stage IV in Fig. 1; Shorvon and Ferlisi, 2011). Propofol or thiopental exert potent anti-inflammatory effects mediated by decreased NF-κB expression (Roesslein et al., 2008; Sanchez-Conde et al., 2008). Interestingly, sevoflurane, which has similar anaesthetic potency but lacks anti-inflammatory action, is not the first choice among halogenated anaesthetics for status epilepticus. Furthermore, sevoflurane may actually have an epileptogenic effect (Jaaskelainen et al., 2003). These anti-inflammatory mechanisms predict prevention of blood–brain barrier disruption or recovery of blood–brain barrier integrity; therefore, these effects may be comparable to what was observed with corticosteroids in status epilepticus or other forms of seizures (Verhelst et al., 2005; Marchi et al., 2009, 2011). Moreover, the authors point out that SRSE elicits as a consequence of stroke, trauma or infection, conditions where blood–brain barrier dysfunction and altered brain homeostasis were demonstrated to play a role.

Another therapeutic approach to refractory status epilepticus reviewed by Shorvon and Ferlisi (2011) is the use of intravenous infusion of magnesium sulphate. Magnesium has negligible blood–brain barrier permeability and in healthy individuals, brain levels exceed serum concentrations (Amtorp and Sorensen, 1974; Heath and Vink, 1998). Under conditions of disrupted blood–brain barrier (e.g. during SRSE), brain Mg2+ concentration may decrease (e.g. as a result of brain-to-blood leakage), leading to N-methyl-D-aspartic acid (NMDA) receptor disinhibition. Systemic administration of high magnesium may restore brain levels of this ion, with a pronounced effect on excitatory synapses and thus on status epilepticus.

The most heterogeneous group of treatments for SRSE includes anti-inflammatory corticosteroids, vagal nerve stimulators, ketogenic diet and hypothermia. All these treatments have beneficial (protective or restorative) effects on the blood–brain barrier, and as predicted by the proposed aetiological role for blood–brain...
barrier disruption in status epilepticus, may terminate seizures by promoting cerebrovascular repair (Table 1).

Last but not least, even traditional antiepileptic drugs exert immunological effects. While an ample array of contradictory data exists, the fact that antiepileptic drugs interfere with the immune system hints at unconventional pathways leading to, or sustaining, seizure activity (Beghi and Shorvon, 2011).

In conclusion, we suggest that even ‘traditional’ or device-based interventions routinely used to treat refractory status epilepticus may act by improving brain homeostasis. This may be achieved by anti-inflammatory effects leading to blood–brain barrier repair. Whether similar mechanisms may be involved in the treatment of non-status epilepticus seizures remains to be investigated.

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**Table 1** Drugs and interventions used to control status epilepticus have anti-inflammatory effects that may result in blood-brain barrier protection/repairing

<table>
<thead>
<tr>
<th>Therapeutic intervention</th>
<th>Classification/Drug class</th>
<th>Accepted mechanism of action</th>
<th>Anti-inflammatory potency</th>
<th>Predicted or demonstrated effects on BBB integrity</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propofol</td>
<td>Anaesthetic</td>
<td>GABA</td>
<td>Inhibits NF-κB</td>
<td>Protection/repair</td>
<td>Jaaskelainen et al., 2003; Sanchez-Conde et al., 2008; Schneemilch et al., 2005</td>
</tr>
<tr>
<td>Thiopental</td>
<td>Short-acting hypnotic agent Anaesthetic</td>
<td>GABA</td>
<td>Inhibits NF-κB</td>
<td>Protection/repair</td>
<td>Roesslein et al., 2008; Schneemilch et al., 2005</td>
</tr>
<tr>
<td>Ketamine</td>
<td>Dissociating anaesthetic NMDA antagonist</td>
<td>Inhibits NF-κB and IL-1β, TNF-α surge</td>
<td>Protection/repair</td>
<td>Beilin et al., 2007; Welters et al., 2010, 2011;</td>
<td></td>
</tr>
<tr>
<td>Magnesium</td>
<td>Electrolyte</td>
<td>NMDA blocker NA</td>
<td>Restores NMDA receptor blockade after BBB disruption</td>
<td>Amtorp and Sorensen, 1974; Heath and Vink, 1998</td>
<td></td>
</tr>
<tr>
<td>Vagal nerve stimulator</td>
<td>Device</td>
<td>Unknown Nicotinic receptors Ghrelin</td>
<td>Nicotinic</td>
<td>Protection/repair</td>
<td>Cheyuo et al., 2011; Rosas-Ballina and Tracey, 2009; Rosas-Ballina et al., 2011</td>
</tr>
<tr>
<td>Ketogenic diet</td>
<td>Dietary regimen</td>
<td>Unknown NA</td>
<td>Protection/repair</td>
<td>Janigro, 1999; Nabbout et al., 2011</td>
<td></td>
</tr>
<tr>
<td>Hypothermia</td>
<td>Medical management</td>
<td>Unknown</td>
<td>Inhibits NF-κB</td>
<td>Protection/repair</td>
<td>Oztas and Kaya, 1994; Polderman, 2009; Webster et al., 2009</td>
</tr>
<tr>
<td>Cortico-steroids</td>
<td>Anti-inflammatory agents</td>
<td>Immunodepression Similar to NFκB inhibition</td>
<td>Protection/repair</td>
<td>Marchi et al., 2009, 2011</td>
<td></td>
</tr>
</tbody>
</table>

BBB = blood–brain barrier; NMDA = N-methyl-D-aspartic acid; NF-κB = nuclear factor kappa B; IL = interleukin; TNF = tumor necrosis factor; NA = not available.

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**References**


