BAY AREA VET MRI
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Reasons why Status Epilepticus progress toward more refractory stages over time

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a) loss of GABA-induced inhibition
b) upregulation of NMDA and AMPA receptors for glutamate
c) BBB transporter overexpression

a) Loss of GABA-induced inhibition

GABAergig drugs (eg, benzodiazepines (BDZs) are used particularly used in the management of SE. BDZs mechanism of action in seizure: pre and post-sinaptic GABA-ergic transmission, they bind on the γ-subunit of $GABA_A$ receptors, enhancing the inhibitory effect of GABA, and resulting in opening of chloride channels and influx of chloride within the neurons. This results in hyperpolarization of the cell membrane and inhibition of nerve impulses.

BDZs effectiveness, may gradually decrease with prolonged seizure activity due to reduced synaptic targets (e.g. internalization of $GABA_A$ receptors γ-subunit, and conversion of receptors subunits to less BDZs-responsive)

Medications that act also on other external sub-units (e.g. α, β) of $GABA_A$ receptors (e.g. phenobarbital, propofol, inhalation anesthetics) should be more efficient in case of BDZs resistant SE.

In refractory and super refractory SE, resistant to most $GABA_A$ – acting drugs may occur due to several factors including phosphorylation and internalization of the potassium-chloride transporter and increased of intracellular chloride.

b) Upregulation of NMDA and AMPA receptors for glutamate

In addition, loss of AMPA receptors $GluA_2$ subunit and overexpression of NMDA receptors occur, which promote glutamate-induced excitation, these changes lead to calcium accumulation within the cells and trigger apoptosis.

Glutamate receptor (NMDA) antagonists (e.g. ketamine) may be beneficial particularly in refractory stages of SE and they may even help preventing resistance, if administered at early stages.

Overexpression and activation of NMDA receptors may also contribute toward calcineurin-induced internalization of the $GABA_A$ receptors γ-subunits, leading further BDZs resistance. Therefore, NMDA receptors inhibitors may also have another benefit by means of enhancing BDZs potency.

c) Overexpression of BBB drug transporters

A significant upregulation by 87%-166% of endothelial P-glycoprotein (PGP; BBB drug transporter) was demonstrated in the canine brain following SE that led to enhanced BBB efflux of antiseizure drugs and limited concentrations of drugs into the brain.

In Conclusion: because of the aforementioned mechanisms, the early application of drugs with different mechanism of action (e.g. $GABA_A$ agonists and NMDA antagonists) and through different routes (e.g. administration routes that might avoid BBB) with the aim to circumvent the mechanism that sustain continuous seizure activity is fundamental for the management of SE.