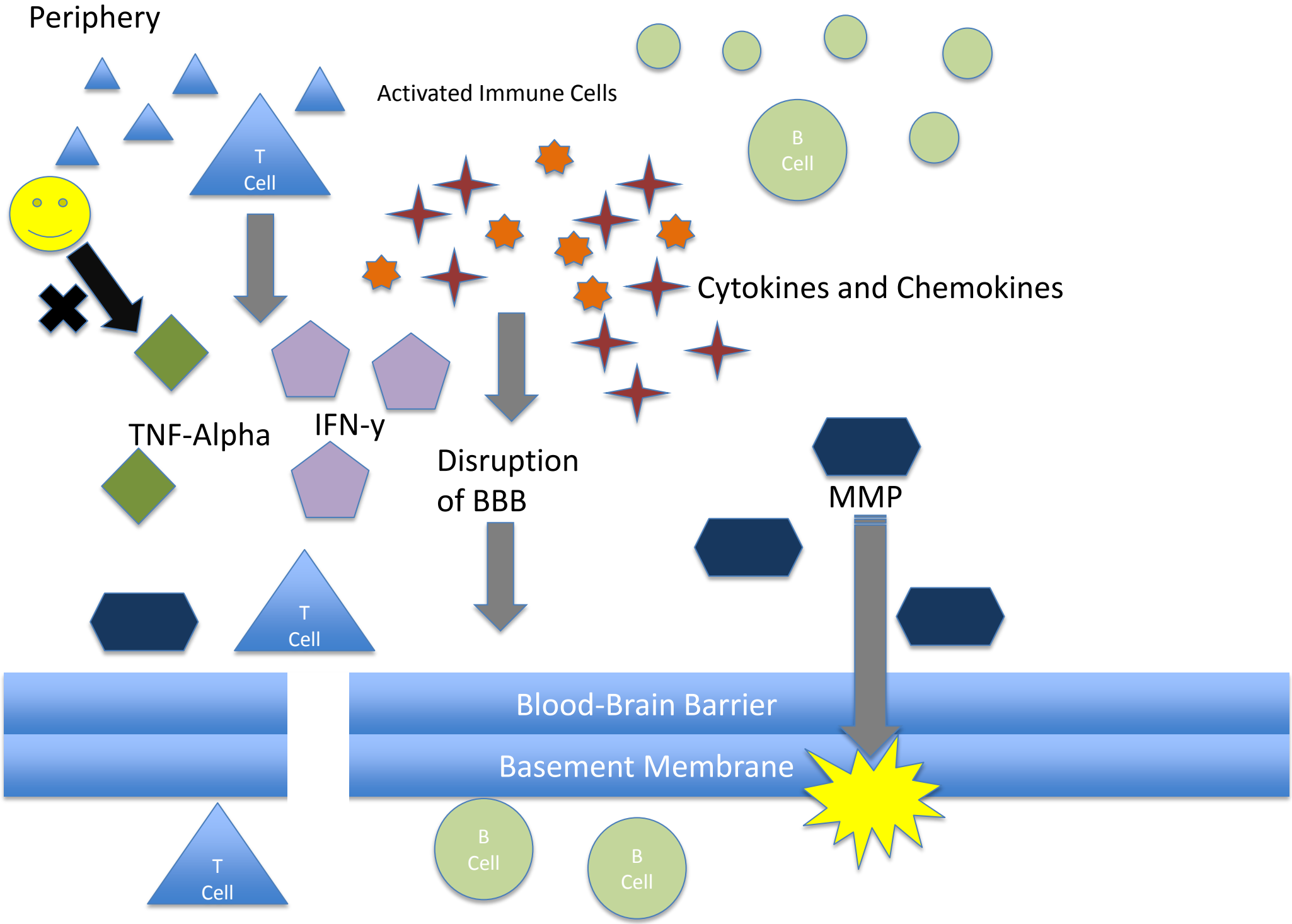
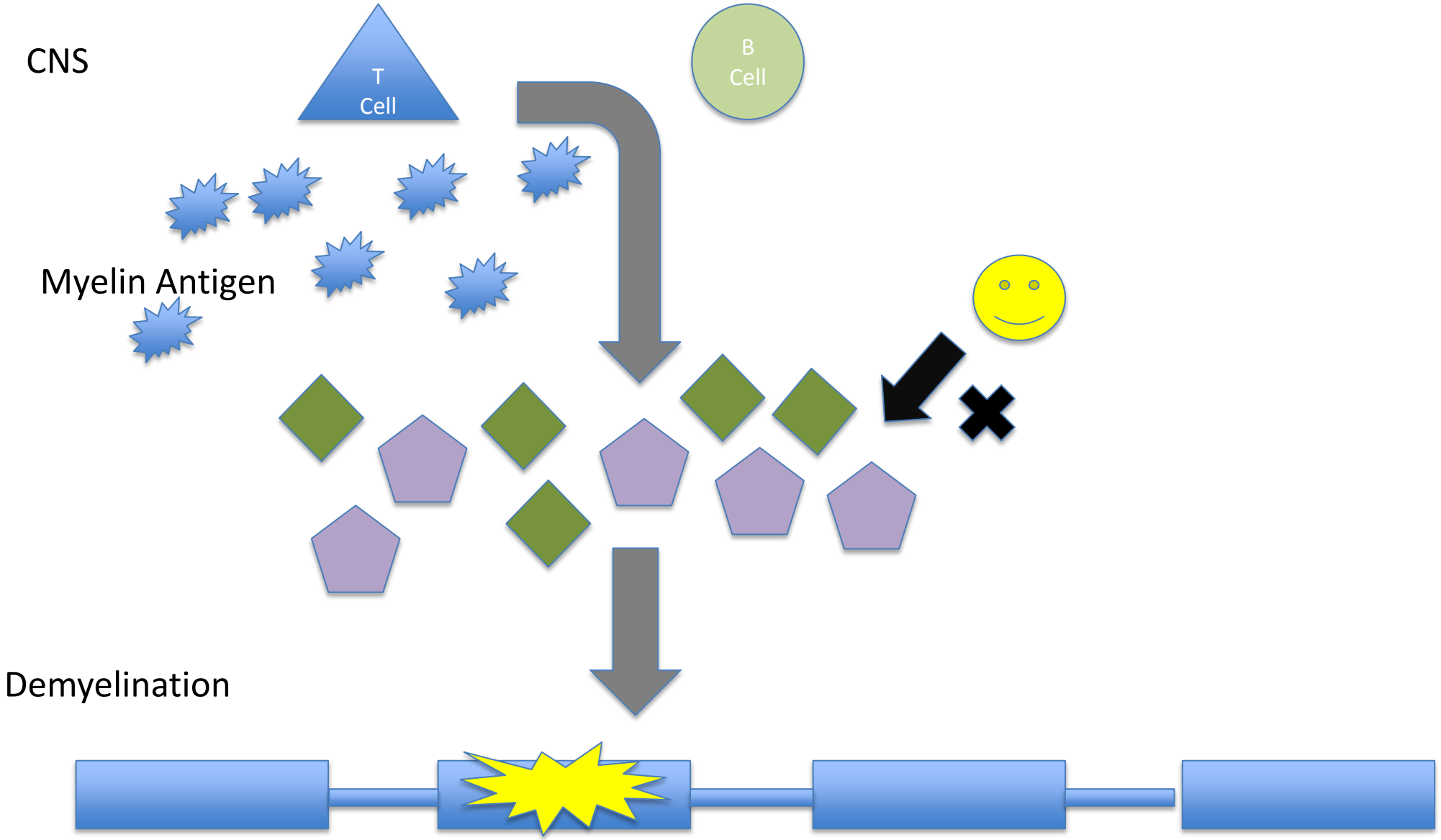
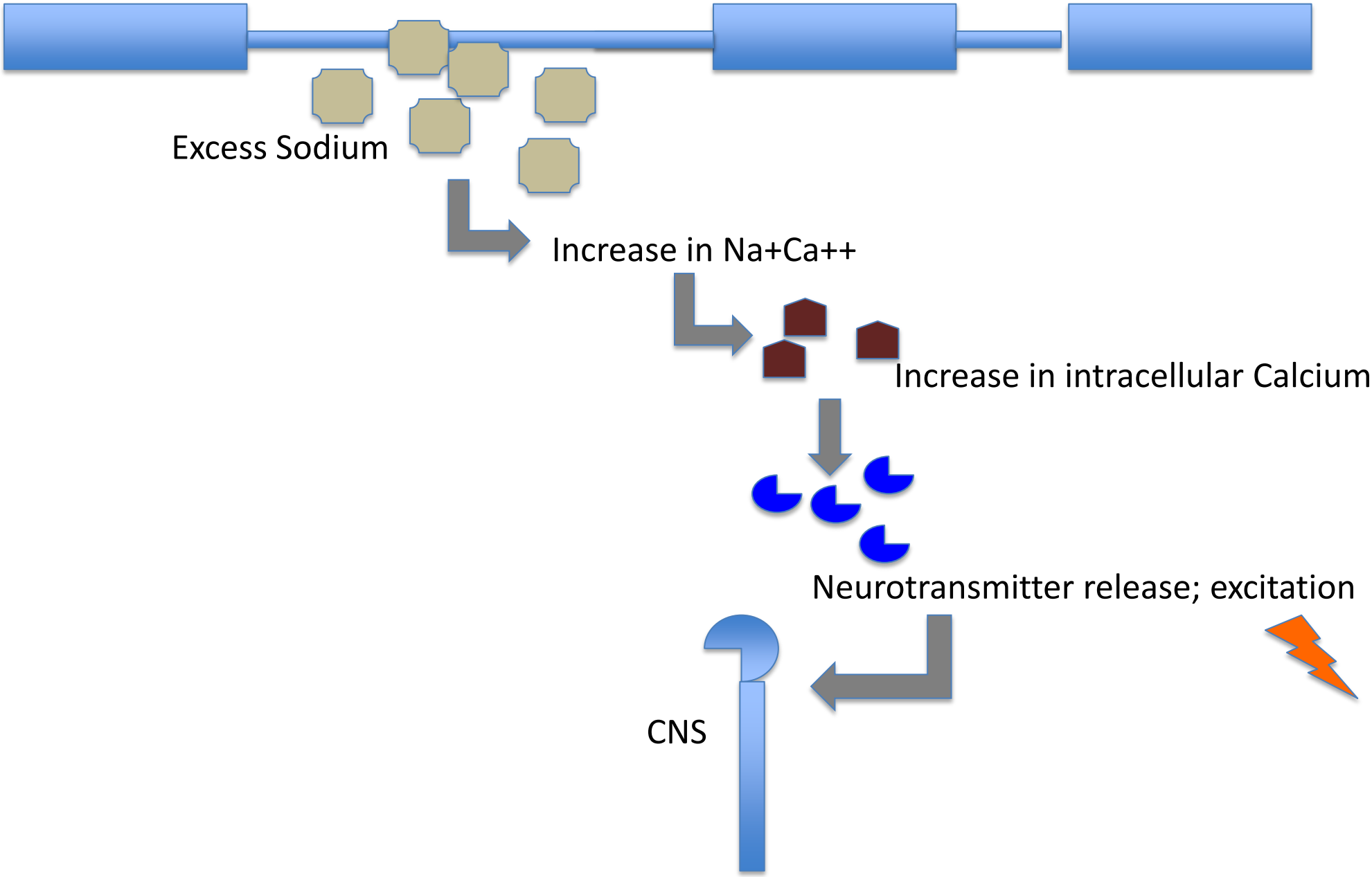
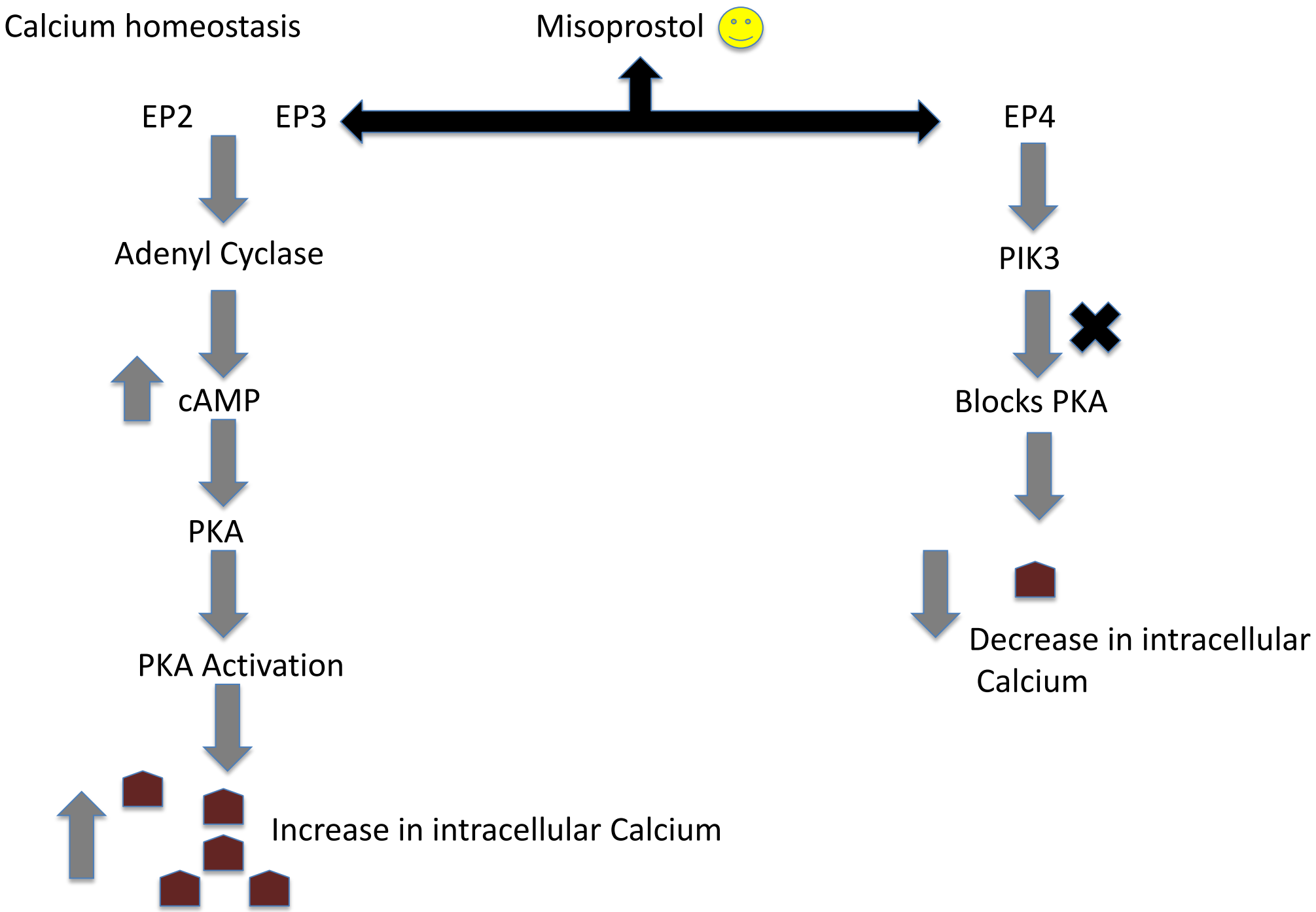

Periphery
Activated Immune Cells
T Cell
B Cell
Cytokines and Chemokines
TNF-Alpha
IFN-y
Disruption of BBB
MMP
T Cell
Blood-Brain Barrier
Basement Membrane
T Cell
B Cell
B Cell


CNS
T Cell
B Cell
Myelin Antigen
Demyelination

Loss of internodal segment




Calcium homeostasis
Misoprostol
EP2
EP3
EP4
Adenyl Cyclase
PIK3
cAMP
Blocks PKA
PKA
PKA Activation
Decrease in intracellular Calcium
Increase in intracellular Calcium

| AED medications and their effects on ion channels in MS | |
|---|---|
| Carbamazepine | Inhibits voltage-gated sodium channels |
| Oxcarbazepine | Inhibits voltage-gated sodium channels |
| Phenytoin | Inhibits voltage-gated sodium channels |
| Lamotrigine | Inhibits voltage-gated sodium channels And calcium channels |
| Topiramate | Inhibits voltage-gated sodium channels, increases GABA and AMPA |
| 4-aminopyridine | Inhibits voltage-gated potassium channels |
| Gabapentin | Inhibits voltage-gated calcium channels, and increases GABA |
| Pregabalin | Inhibits voltage-gated calcium channels, and increases GABA |

**BACKGROUND:** Painful tonic spasms may occur in association with multiple sclerosis (MS) and have recently been reported to occur even more frequently in people with neuromyelitis optica (NMO). Painful tonic spasms (PTS) are paroxysmal episodes associated with sustained abnormal tonic posture. The spasms are often triggered by movement but also occur after sensory stimulation or spontaneously. They may be induced in some patients by hyperventilation. They usually begin in one limb and may spread to involve the ipsilateral limb or the face. Spasms are usually under 2 minutes in duration; however, they may occur numerous (sometimes >50) times per day. These recurrent events are not only disabling but usually quite painful. They are commonly treated with anticonvulsant agents, although baclofen and corticosteroids may also be tried. Although PTS may spontaneously subside, they may be long-standing and refractory to therapy. We present a case report describing use of misoprostol with dramatic benefit.

**OBJECTIVES:** We describe use of misoprostol to control refractory painful tonic spasms in a patient with NMO.

**METHODS:** Single case report.

**RESULTS:** The patient is a 59-year-old woman diagnosed with seropositive NMO in 2005. Her disease is currently under control with rituximab given every 3 months. She has experienced PTS throughout her disease course and has never achieved complete remission of the PTS. Her PTS usually involve her right leg and may spread to involve her arm and cause her head to turn to the right. Tone may also become increased in her left leg. These events interfere with function and make it difficult for her to leave the home and function in the community. Events would occur up to 60 times per day. She was initially treated with carbamazepine, which resulted in a marked decrease in but not total control of her events. Upward dose titration to 1800 mg per day was associated with ataxia. She was switched to oxcarbazepine without additional benefit (and the development of hyponatremia). Prior treatment with gabapentin up to 1800 mg per day and levetiracetam up to 5000 mg per day also did not stop her events. Her best control was 5 to 6 episodes per day. These medications were associated with side effects including sedation. Prior courses of methylprednisolone were associated with transient reductions in PTS as well. Because of continued disabling PTS, she was treated with misoprostol 200 μg three times per day. Within 1 day of starting this agent, fully expressed dystonic spasms had stopped, and this situation has continued for 8 weeks. She continues to have an occasional episode of mild right foot dystonia.

**CONCLUSIONS:** This case demonstrates a marked benefit from using misoprostol for control of PTS. The agent was selected because of noted benefits of its use for trigeminal neuralgia, another type of ephaptic phenomenon seen in people with MS and related disorders. We will discuss possible mechanisms of action.

**PTS pathophysiology**

The pathophysiology of painful tonic spasms (PTS) remains unclear. Two principals remained consistent among theories after an event of demyelination resulting in a lesion within the CNS; inflammation and axonal irritability. Lesions are associated with infiltration of lymphocytes, macrophages, and cytokines (5,7). This inflammatory mediated response results in axonal irritability and transverse ephaptic conduction. As Ostermann and Westerberg proposed, PTS in MS develop from axonal irritability secondary to the release of cytokines or by an ephaptic spread of action potentials within a demyelinating lesion (18). This was supported by a study using transcranial magnetic stimulation that divulged that ephaptic activity of axons within the demyelinating lesions in corticospinal fibers is responsible for PTS (26). Ion channels also may play an important role. It is known that demyelination causes a disruption in the influx and efflux of sodium, potassium, and calcium. Due to the loss of myelin the action potential is required to extend a longer axonal distance. There is an increase in intracellular calcium concentration. When calcium channels open during depolarization the influx of calcium leads to additional depolarization by opening other voltage-gated channels. Moreover, this process may result in the release of neurotransmitters. Neurotransmitters may then bind to receptors that facilitate additional excitation. One particular calcium channel subtype, Cav2.2, transmits pain signals from afferent neurons to neurons with the CNS. PTS have been associated with lesions in the brain (basal ganglia, thalamus, internal capsule, cerebral peduncles, medulla), and spinal cord.

PTS is typically responsive to anti-epileptics such as carbamazepine, oxcarbazepine, and others (see Table 1). These medications are able to decrease neuronal over activity via effects on voltage gated ion channels resulting in hyperexcitability and ephaptic conduction. Our patient failed carbamazepine, oxcarbazepine, and was most recently on levetiracetam but with breakthrough PTS. Based on the reports by Redar et al and Stefan et al, the use of misoprostol to treat another paroxysmal event that is seen in multiple sclerosis, trigeminal neuralgia, we decided to try misoprostol for refractory PTS in our patient (13, 14). Our patient was then started on misoprostol 200 mcg three times daily and had complete resolution of PTS within two days.

**MOA misoprostol**

The mechanism of action of misoprostol in PTS is unclear. Misoprostol is a prostaglandin E1 analogue used to prevent gastrointestinal bleeding in patients taking nonsteroidal anti-flammatories (NSAIDs). Prostaglandins belong to the family of signaling molecules known as eicosanoids, which are derived from the oxidation of fatty acids. Saturated fatty acids are capable of crossing the blood-brain barrier via the probenecid-sensitive transport system. Once within the CNS, fatty acids can then be oxidized into various substances, including; the eicosanoids (8). Prostaglandins elevate cyclic adenosine monophosphate (cAMP), which inhibits monocyte function and selectively blocks secretion of cytokines by subsequently decreasing other inflammatory mediators (14, 23). Several cytokines are involved in the initiation and maintenance of inflammation including IL-1 and TNF. Misoprostol inhibits the proliferation of IL-1 with mouse thymocytes, inhibits the production of TNF, and inhibits levels of INF-y (9). One study showed that long-acting prostaglandin inhibited clinical and histological experimental autoimmune encephalomyelitis (EAE) which is the animal model for multiple sclerosis (23). Therefore, inflammation and axonal irritability might be reduced by misoprostol leading to improvement, or in our case, resolution of PTS.

Another mechanism by which misoprostol works is through the activation of prostaglandin receptors that can alter levels of intracellular calcium. There is evidence that misoprostol supports the restoration of intracellular calcium homeostasis via activation of receptors that are used by prostaglandin, these receptors include: EP2, EP3, and EP4. The receptor that is activated determines the effect on levels of intracellular calcium. If calcium is altered this may be able to result in less excitation.

**Conclusion**

Though PTS is rare in patients with demyelinating disease, it can be incapacitating. Fortunately, some are treated successfully with anti-epileptics or resolve spontaneously; however, in those who are intolerable to side effects or have no relief, misoprostol is a safe tolerable alternative. Though more information is needed, we encourage the use of misoprostol in patients with demyelinating disease and inadequate control of PTS.

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