MYASTHENIA GRAVIS

Prepared By

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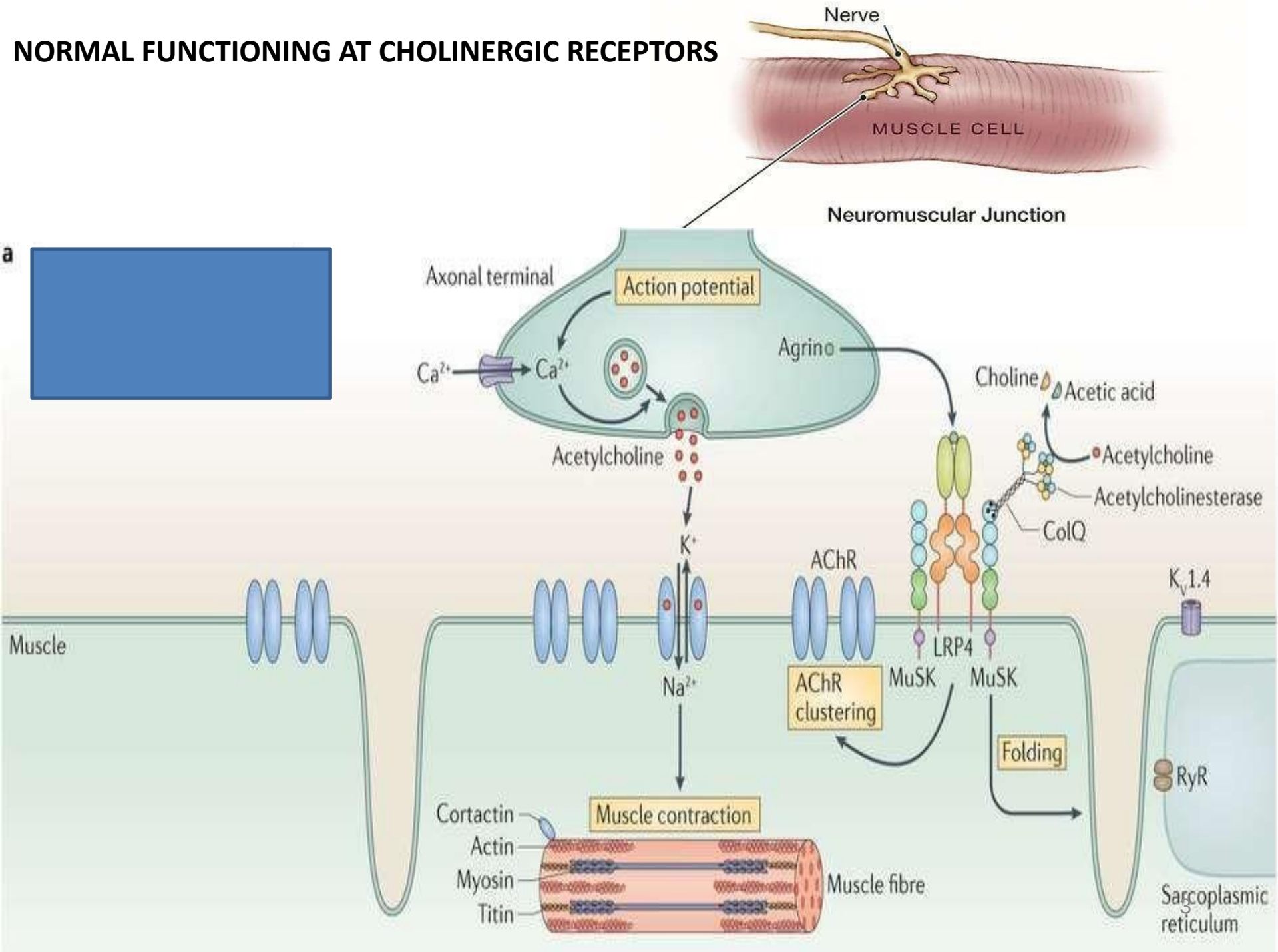
- Derived from Latin and Greek

Myasthenia – weakness

Gravis – serious

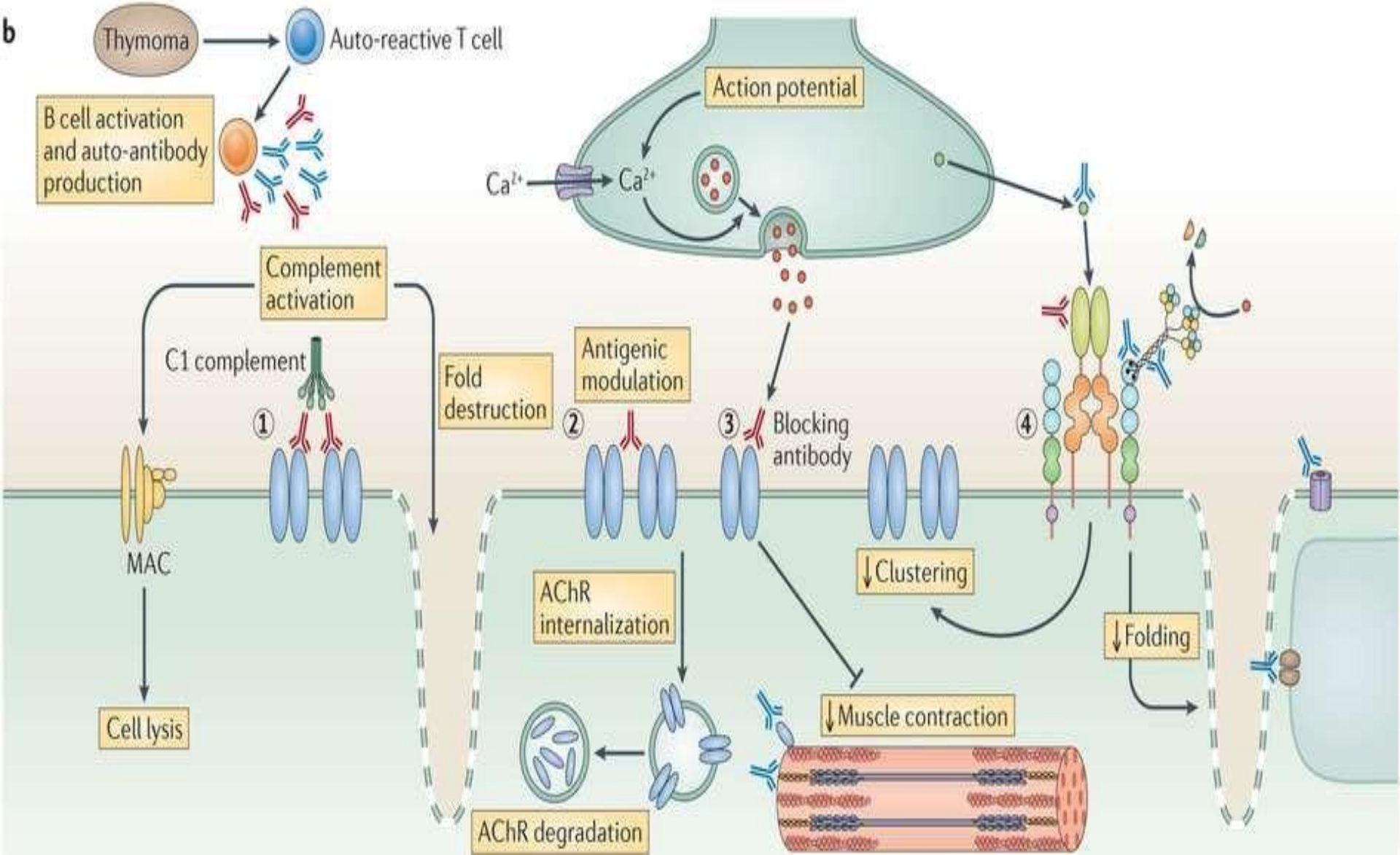
- It means "grave muscle weakness"
- Myasthenia gravis (MG) – It is an autoimmune disorder - antibodies against acetylcholine receptors at neuro muscular junction are developed.
- These antibodies attack and destroy acetylcholine receptors and postsynaptic molecules
- It leads to impaired signal transduction which causes muscle weakness and fatigue.

NORMAL FUNCTIONING AT CHOLINERGIC RECEPTORS



PATHOPHYSIOLOGY

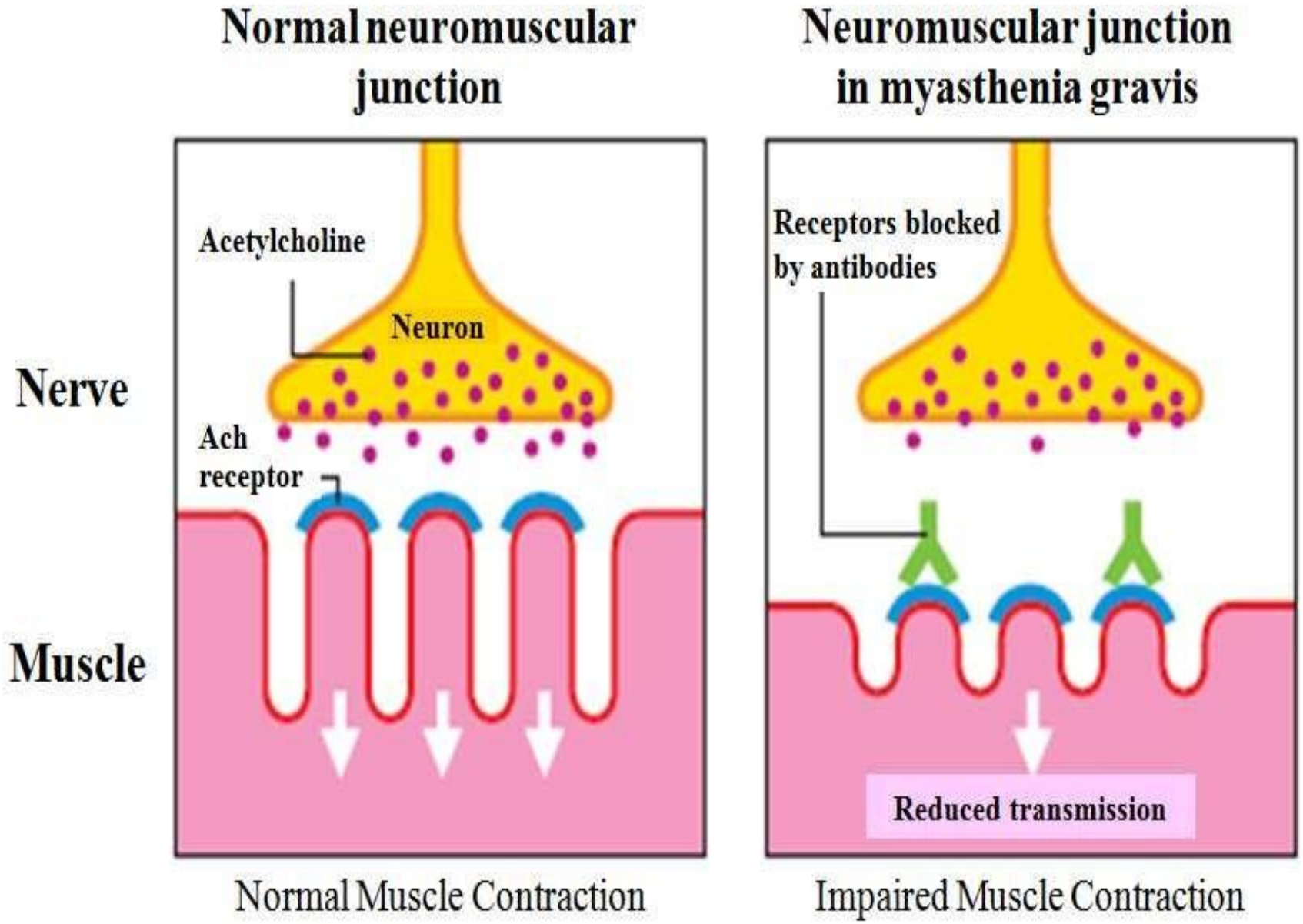
Antibodies are directed towards acetyl choline receptors at neuro muscular junction.



The antibodies act by different mechanisms:

1. Blocks the binding of ACh to the AChR.
2. Increases the degradation rate of AChR
3. A complement-mediated destruction

- Results in:
  - ↓ nicotinic acetylcholine receptors
  - ↓ postsynaptic membrane folds
  - Widened synaptic cleft


Normal neuromuscular junction
Neuromuscular junction in myasthenia gravis
Nerve
Muscle
Acetylcholine
Neuron
Ach receptor
Receptors blocked by antibodies
Reduced transmission
Normal Muscle Contraction
Impaired Muscle Contraction

EPIDEMIOLOGY

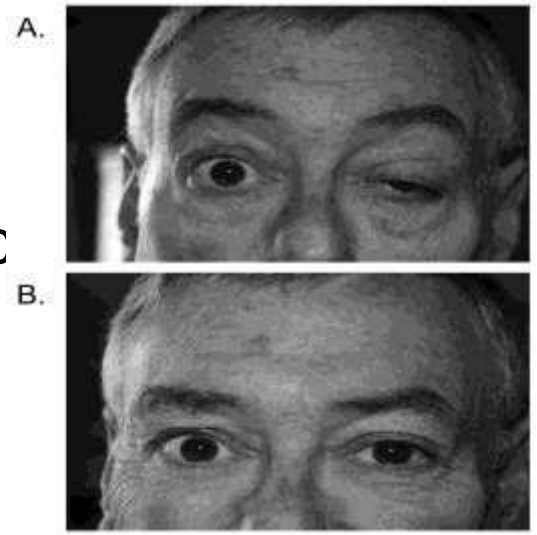
- Prevalence: 1-7 in 10,000
- Age:
- 20-30 yrs (young women), 50-60 yrs (older men)
- < 10% occur in children <10 yrs
- Overall F:M = 3:2
- More common in patients with family history of one or the other autoimmune diseases

SIGNS & SYMPTOMS

- Fluctuating painless weakness
- Worses with repetitive activities an
  - Ocular muscle weakness (85%) Asymmetric

    Ptosis

    Diplopia is very common



Weakness of face and throat muscles

Dysphagia – difficulty in swallowing

Dysarthria – Slurry speech

Dysphonia – difficulty in speaking due to disorder in mouth, throat or tongue.

- Enlarged thymus gland
- Limb muscle weakness
  - Neck extensors > flexors
  - Upper limbs > lower limbs

- Respiratory weakness
  - ❑ Weakness of the intercostal muscles and the diaphragm
  - ❑ Collapsed upper airway
  - ❑ Neuromuscular emergency – mechanical ventilation

Dropped head syndrome

PROGRESSION OF DISEASE

- Mild to more severe over weeks to months
  - Usually spreads from ocular → facial → bulbar → truncal → limb muscles
  - The disease remains ocular in 16% of patients
  - Death rate reduced from 30% to <5% with pharmacotherapy and surgery

DIAGNOSIS

Edrophonium (Tensilon test)

- Initial IV dose of 2 mg of edrophonium is given
- Observed for objective improvement in muscle weakness
- Definite improvement occurs-the test is considered positive & terminated
- If no improvement in weakness - the remainder 8mg of the drug is injected.

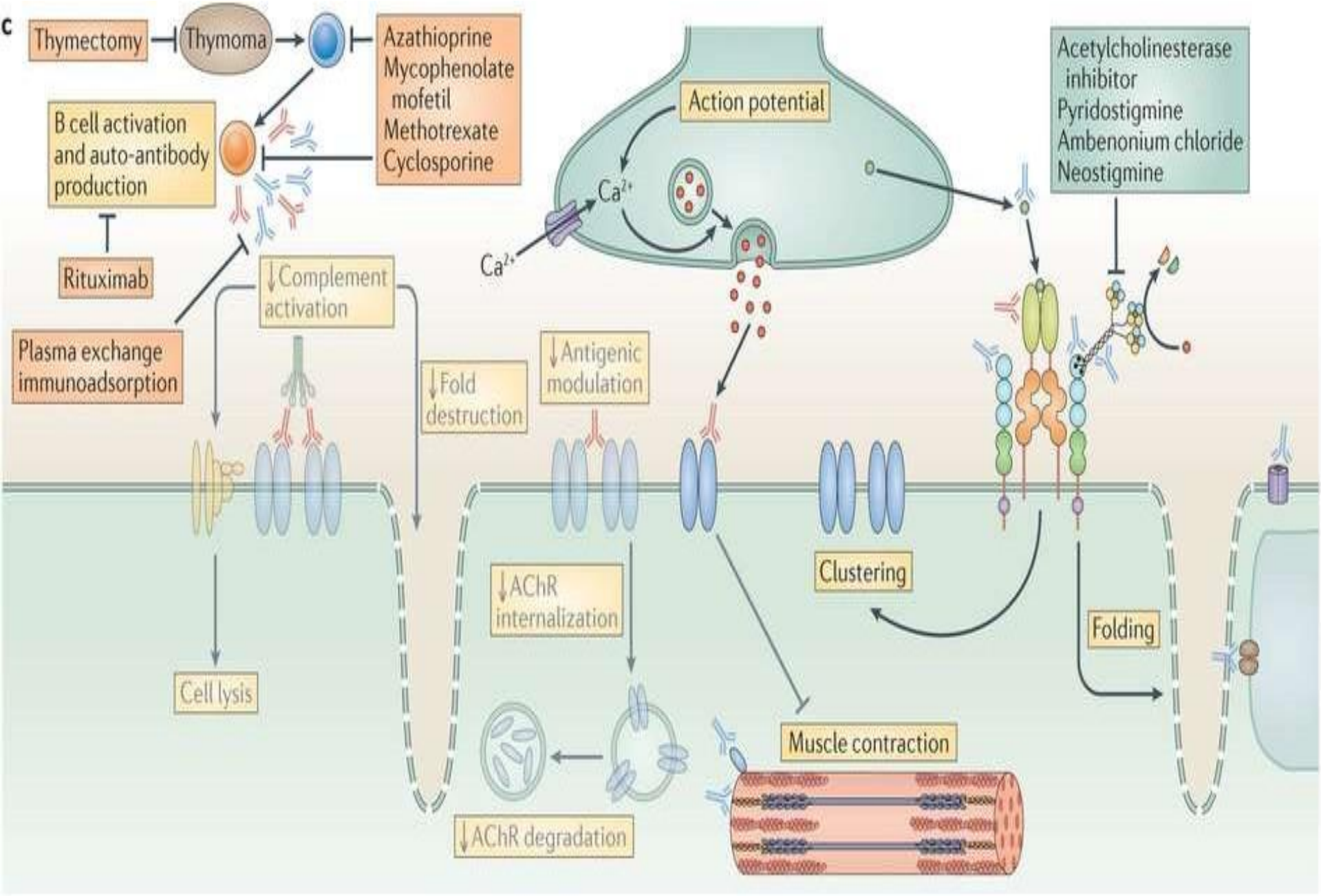
MYASTHENIC CRISIS

- Exacerbation of weakness - endangered life
- Respiratory failure (diaphragmatic and inter costal muscle weakness)
- Cause – intercurrent infection
- Cholinergic crisis – Treated by excessive anticholinesterase medication

Treatment

There are four basic therapies:

- Rapid short-term - plasmapheresis and intravenous immunoglobulin
- Symptomatic treatment - acetylcholinesterase inhibitors
- Chronic long term - immunomodulating treatment - glucocorticoids & immunosuppressive drugs
- Surgical treatment



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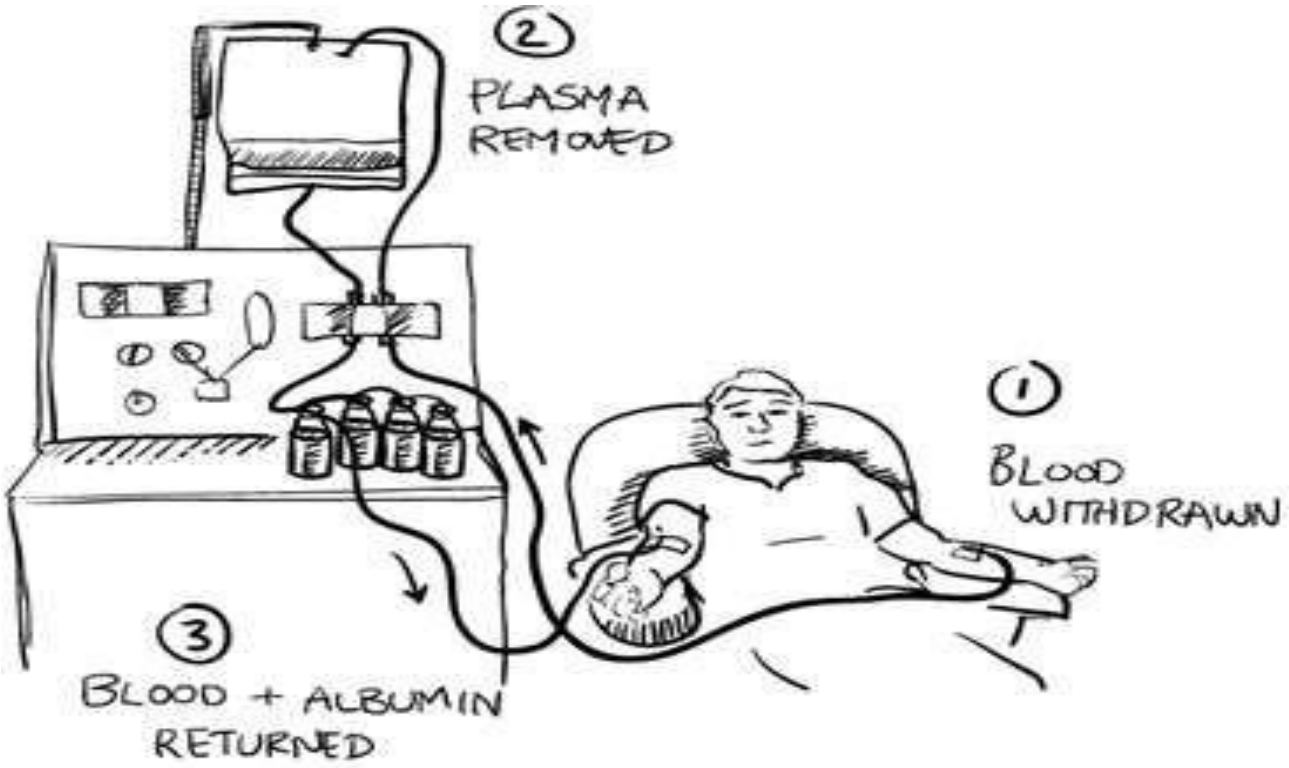
Plasmapheresis



Plasma exchange (PLEx)

PLASMAPHERESIS

- Removes acetylcholine receptor antibodies from blood circulation.
- Rapidly Improves strength.
- Used for
  - short-term intervention
  - Sudden worsening of myasthenic symptoms
  - Chronic intermittent treatment for refractory cases
- Typically one exchange is done every other day for a total of four to six times
- Improvement is noted in a couple of days, but it does not last for more than 2 months.
- Complications – hypocalcemia, hypomagnesemia, hypothermia, hypotension & transfusion reactions

Intravenous Immunoglobulin Therapy

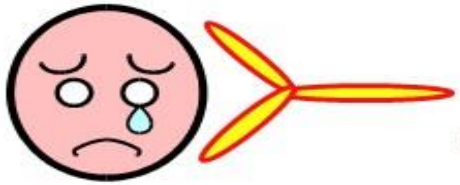
- Rapid improvement
- Used to treat Severe myasthenic weakness
- Dose is 2 g/kg over 5 days (400 mg/kg per day)
- Improvement occurs in ~70% of patients
- Adverse reactions include headache, fluid overload, and rarely aseptic meningitis or renal failure

Intravenous Immunoglobulin Therapy

How does IVIg work in MG?

One possible mechanism

Acetylcholine receptor

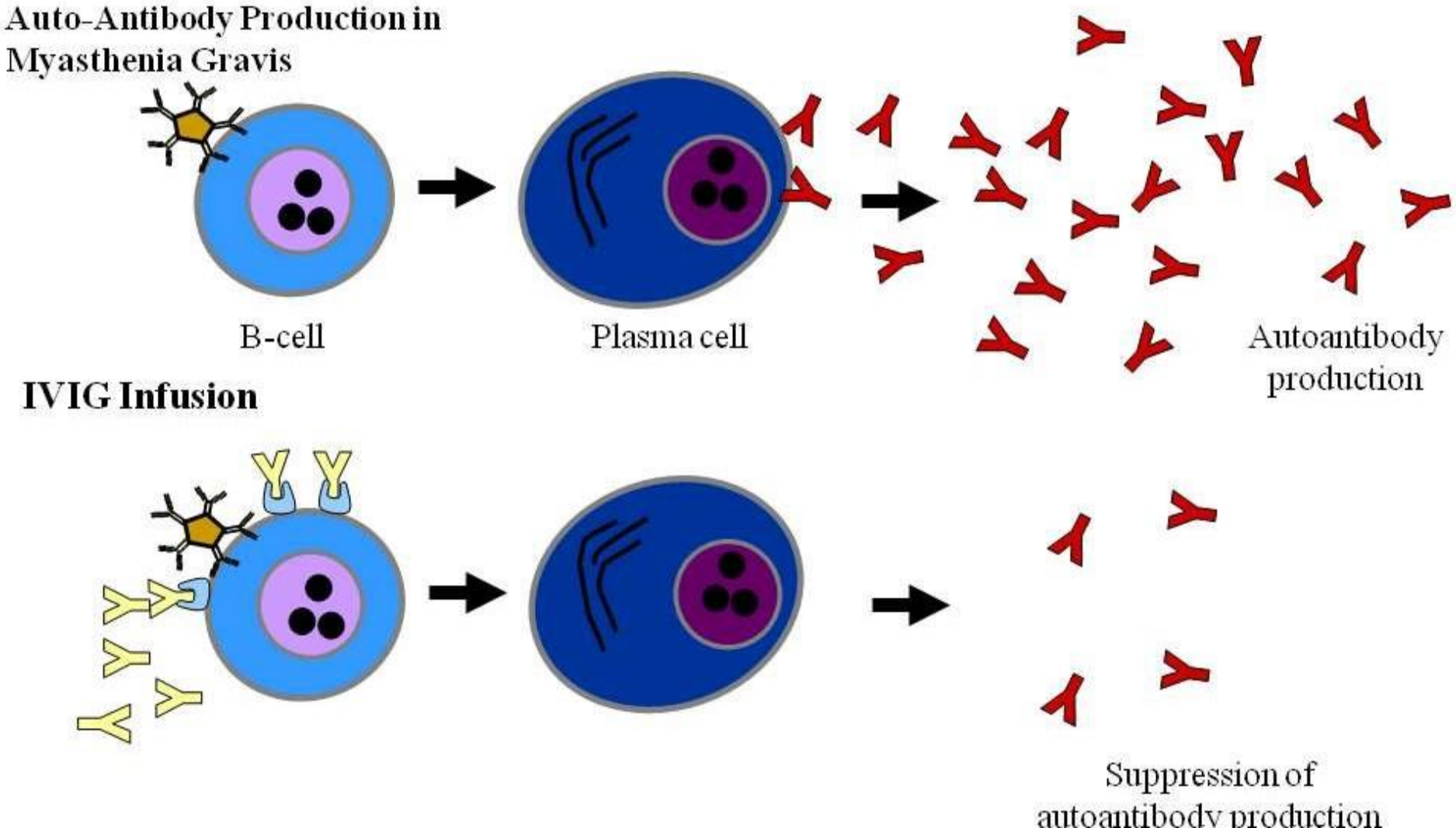


'Bad' antibody against AChR

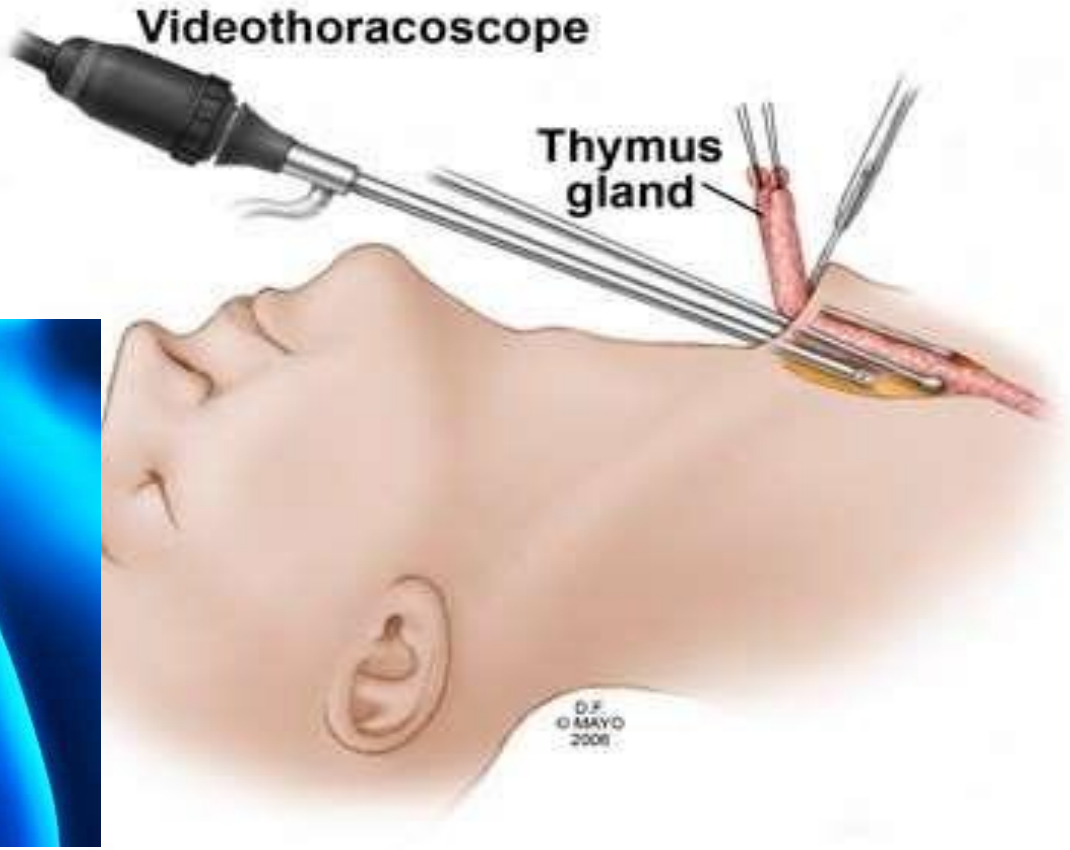
IVIg infusion

'Good' antibodies against bad antibodies

The presence of large amounts of IgG will also suppress the production of host IgG



Thymectomy



Thymectomy

- Carried out in all patients with generalized Myasthenia gravis - aged between puberty and 55 years
- Thymoma - Surgical removal is a must - possibility of local tumor spread
- Up to 85% of patients experience improvement after thymectomy
- Of these, ~ 35% achieve drug-free remission

Anticholinesterase Medications

•Treatment is usually started with *neostigmine* 15 mg orally 6 hourly.

•Dose and frequency is then adjusted to obtain optimum relief from weakness.

•However, the dosage requirement may fluctuate from time to time and there are often unpredictable periods of remission and exacerbation.

•Pyridostigmine is an alternative which needs less frequent dosing.

•If intolerable muscarinic side effects are produced, atropine can be added to block them.

•These drugs have no effect to restore muscle strength adequately when used alone.

- Onset - 15–30 min and lasts for 3–4 h
- Dose - 30–60 mg three to four times daily

Immunosuppression

- Is required in nearly all pts with

  -late-onset MG

  -thymoma MG

  -MuSK-MG

- Suppress autoantibody production & its detrimental effects at NMJ

Corticosteroids:

- Shows immunosuppressant action.
- They inhibit production of antibodies.
- However, their long term use has problems of its own.
- Prednisolone 30–60 mg/day induces remission in about 80% of the advanced cases.
- 10 mg daily or on alternate days can be used for maintenance therapy.
- Both azathioprine and cyclosporine also inhibit antibody synthesis by affecting T-cells.
- But response to azathioprine is slow in onset (takes upto 1 year).
- Cyclosporine shows effect relatively quick (in 1–2 months).

Glucocorticoids

- First & most commonly used immunosuppressant
- Used when symptoms of MG are not adequately controlled by cholinesterase inhibitors alone
- MOA- inhibits MHC expression & IL-1 production

  ⇩ IL-2 & IFNγ production

Mycophenolate mofetil

- Choice for long-term treatment
- MOA-prodrug of mycophenolic acid

  - Inhibits inosine monophosphate dehydrogenase
- Lymphocyte proliferation, antibody production and Cell mediated immunity are inhibited

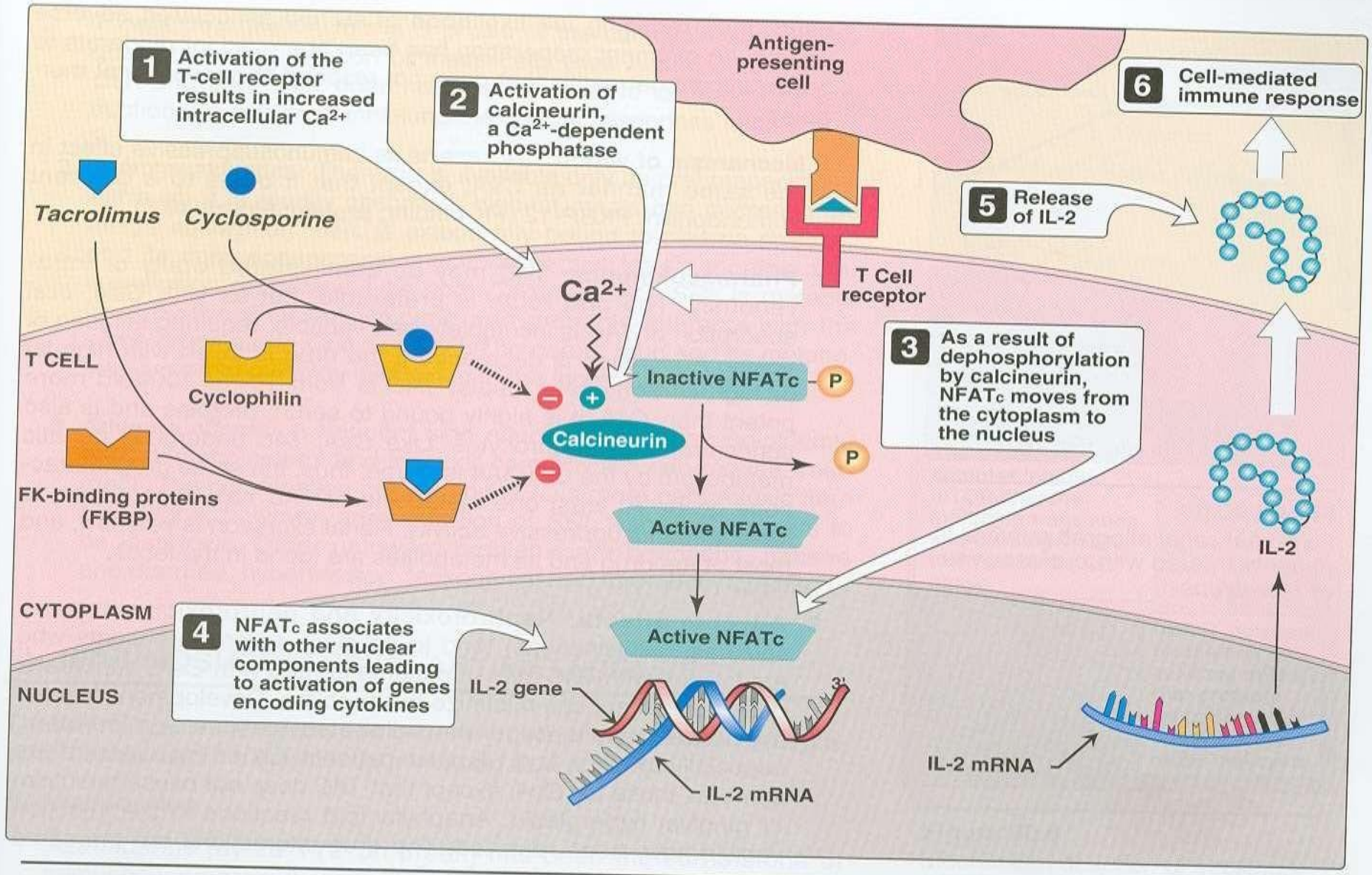
- Does not kill or eliminate preexisting autoreactive lymphocytes
- Clinical improvement may be delayed for 2-6 months
- Vomiting, diarrhoea, leucopenia and predisposition to infection, g.i. bleeds are the prominent adverse effects.

Azathioprine

- It is a purine analog, reduces nucleic acid synthesis, thereby interfering with T-and B-cell proliferation
- Is effective in 70%–90% of patients with MG
- When used in combination with prednisone - more effective & better tolerated than prednisone alone
- Beneficial effect takes at least 3–6 months to begin

Calcineurin inhibitors

- **Cyclosporin -** Used mainly in patients who do not tolerate or respond to azathioprine
- Blocks synthesis of IL-2 cytokine
- Dose 4–5 mg/kg per day
- Cyclosporine can cause nephrotoxicity, neurotoxicity, hepatotoxicity, hyperlipidemia, hyperuricemia, hyperglycemia, hirsutism and gum hyperplasia


1 Activation of the T-cell receptor results in increased intracellular Ca2+
2 Activation of calcineurin, a Ca2+-dependent phosphatase
Antigen-presenting cell
6 Cell-mediated immune response
Tacrolimus
Cyclosporine
5 Release of IL-2
T Cell receptor
Ca2+
T CELL
Cyclophilin
Inactive NFATc
P
3 As a result of dephosphorylation by calcineurin, NFATc moves from the cytoplasm to the nucleus
Calcineurin
FK-binding proteins (FKBP)
Active NFATc
IL-2
CYTOPLASM
4 NFATc associates with other nuclear components leading to activation of genes encoding cytokines
Active NFATc
NUCLEUS
IL-2 gene
3'
IL-2 mRNA
IL-2 mRNA

Tacrolimus

- Is ~ 100 times more potent than cyclosporin
- It binds to FK506 binding protein (FKBP) and causes inhibition of helper T cells
- Beneficial effect appears more rapidly than that of azathioprine
- less nephrotoxicity, hirsutism, hyperlipidemia than cyclosporine
- Dose - 0.1 mg/kg per day

Treatment	Time to Clinical Effect
Pyridostigmine	10–15 minutes
Plasmapheresis	1–14 days
IVIg	1–4 weeks
Prednisone	2–8 weeks
Mycophenolate mofetil	2–6 months
Cyclosporine	2–6 months
Azathioprine	3–18 months