DRUGS ACTING ON NMJ

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LEARNING OUTCOMES

By the end of the lecture, students will be able to...

1. list the drugs/agents that influence the neurotransmission at the neuromuscular junction
2. list the types of neuromuscular blockers
3. describe the pharmacological profile of drugs acting on the neuromuscular junction.
4. describe the basis of the use of acetylcholinesterase inhibitors in myasthenia gravis and reversal of the effects of muscle relaxants
OUTLINE....

A. Neuromuscular Junction

B. Nicotinic Receptors

C. Neuromuscular Blocking Agents

D. Botulinum Toxin

E. Acetylcholinesterase Inhibitors
NEUROMUSCULAR TRANSMISSION

- Nerve Impulse from Somatic motor nerve
- Release of Ach from nerve ending
- Ach binds to Nicotinic receptors
- Depolarize muscle fibres
- Muscle Contraction
NICOTINIC RECEPTORS

Large doses of ‘Nicotine’ acts as agonists to this group of cholinergic receptors.

These are found at
a) Sympathetic and Parasympathetic Ganglia.
b) At Neuromuscular Junction
c) At CNS
d) At Adrenal Medulla
DRUGS ACTING AT NMJ

- Neuromuscular blocking drugs
  - Tubocurarine
  - Suxamethonium

- Acetylcholinesterase inhibitors
  - Edrophonium
  - Neostigmine
NEUROMUSCULAR BLOCKING DRUGS

1. Competitive Neuromuscular Blocking Drugs.
   e.g. Tubocurarine
        Atracurium
        Pancuronium
        Vecuronium

2. Depolarizing Neuromuscular Blocking Drugs
   e.g. Suxamethonium
        (Succinylcholine)
COMPETITIVE NEUROMUSCULAR BLOCKING DRUGS

These are competitive antagonists of nicotinic acetylcholine receptors at NMJ

- Binds to nicotinic receptors at motor end plate
- Prevents Ach binding and causing depolarization in muscle fibers
- Flaccid Paralysis
TUBOCURARINE

Paralysis in order of:

- muscles of eyelids
  ↓
- muscles of swallowing and speech
  ↓
- muscles of limbs and trunk
  ↓
- respiratory muscles
  (intercostal muscles & diaphragm)
TUBOCURARINE

• Does not cross the blood-brain barrier

  No effect on level of consciousness
  Has no analgesic properties

• Partial blockade at autonomic ganglia and at the adrenal medulla

  Hypotension and tachycardia
TUBOCURARINE

- Stimulates Mast Cells and Release Histamine
  - Bronchospasm
  - Hypotension
  - excessive bronchial and salivary secretion
TUBOCURARINE

- Poorly absorbed from gut ⇒ administered i.v.
- Widely distributed in the body
- Doesn’t cross placenta, blood brain barrier
- Onset in ~ 6 minutes and effects last from 40-80 minutes.
- It is not metabolised.
- It is excreted via the bile (30%) and urine (70%).
TUBOCURARINE

Adverse Effects:

1. Hypotension – Due to blockage of autonomic ganglia and due to histamine release
2. Bronchospasm
3. Flushing
4. Skin Rash
5. Tachycardia

Due to histamine release
Clinical Use:
- For endotracheal intubation
- In abdominal surgery (with GA)
- In patients undergoing IPPV at ICUs
- In the treatment of Tetanus
PANCURONIUM

- Long acting competitive NM blocker (duration of effect 60-120 minutes)
- Elimination - Renal and hepatic
- Lacks Histamine releasing effect
- Blocks muscarinic receptors (Vagolytic Effect) → Hypertension
ATRACURIUM

- Intermediate acting competitive NM blocker (~ 45 min)
- Also cause histamine release to a lesser extent
- Metabolized by,
  a. Hofmann elimination (spontaneous degradation in plasma and tissue at normal body pH and temperature)
  b. ester hydrolysis (catalysis by nonspecific esterases)
- Can be used in patients with liver/kidney failure
REVERSAL OF COMPETITIVE NEUROMUSCULAR BLOCKAGE

Achieved by Cholinesterase inhibitors
  e.g. Neostigmine

Inhibition of Cholinesterase → Accumulation of acetylcholine

Displace competitive blockers & occupy the nicotinic receptors
REVERSAL OF COMPETITIVE NEUROMUSCULAR BLOCKAGE

Practical points:

• An antimuscarinic drug is given prior to neostigmine.

• Action short lived (~ 30 min). Repeated doses may need to be given.
DEPOLARIZING NEUROMUSCULAR BLOCKERS

Suxamethonium (Succinylcholine)
- Acts as an agonist for nicotinic receptors at NMJ

Depolarizing (Phase I) Block:

Initially Depolarization + Muscle contraction

Persistent Depolarization

Motor endplate becomes non excitable

Muscle Relaxation
DEPOLARIZING NEUROMUSCULAR BLOCKERS

Suxamethonium (Succinylcholine)
With prolonged exposure to succinylcholine,

Phase II Block:
- Similar in behaviour to competitive NM blockage
SUXAMETHONIOM

- Has a rapid onset of action. (~1-1.5 minutes)
- But effect very short lived (~5 minutes)
- Effects wears off when suxamethonium degraded by,
  
  butyrylcholinesterase - in the liver
  pseudocholinesterase - in plasma

- Cholinesterase Inhibitors can not reverse the paralysis but worsens it.
Clinical Use:

a. To facilitate endotracheal intubation for artificial ventilation

b. To paralyze skeletal muscles during electroconvulsive therapy for mental disorders

c. In orthopaedic Surgery for short procedures like correction of dislocations
SUXAMETHONIUM

عناصر سلبية

- ضغطة عضلات
- ارتفاع نسبة الكالسيوم
- سpasم الرئة (بسبب إطلاق هيستامين)
- ضربة ضربة القلب المؤقتة (بسبب تفريز العصبونات الغائلا)
- ارتفاع ضغط الدم وسرعات القلب (بسبب تفريز الأنسجة العضلاتية)
SUCCINYLCHOLINE INDUCED HYPERKALAEMIA

Suxamethonium causes efflux of potassium ions via activating nicotinic receptors at NMJ

Loss of muscle excitation
- Upper or lower motor neuron defect
- Disuse atrophy

up regulation and spread of AChRs throughout the whole muscle membrane

Increased efflux of potassium
SUXAMETHONIUM

Adverse effects

- Malignant Hyperthermia (Potentially lethal)
- ↑ Intraocular Pressure
- Myoglobinuria/myoglobinuric
- Succinylcholine in susceptible individuals also induces trismus-masseter spasm(↑ jaw muscle tone)
MALIGNANT HYPERThERMIA

An uncommon pharmacogenetic disorder of muscle induced by exposure to suxamethonium and all the volatile anaesthetic agents.

Administration of triggering agents leads to an uncontrolled release of free calcium from the sarcoplasmic reticulum of skeletal muscle.

Susceptibility is inherited as an autosomal dominant condition.
MALIGNANT HYPERTHERMIA

Clinical features:
1. Hypermetabolism (increased CO2 production, tachycardia, ↑ body temperature)
2. Muscle rigidity
3. Rhabdomyolysis (raised plasma CK and myoglobinuria)

Treatment:
Intravenous administration of dantrolene - blocks Ca^{2+} release from the sarcoplasmic reticulum of skeletal muscles
BOTULINUM TOXIN

- Irreversibly blocks acetylcholine release from cholinergic nerve endings
- Used in cosmetic surgery – facial enhancement
- Used as local injections in the Rx of involuntary muscle spasms
  e.g. facial spasm, blepharospasm, dystonias
MODE OF ACTION BOTULINUM TOXIN A

Selective binding & internalization into Ach presynaptic neuron

Binds to the SNARE protein complex and causes proteolysis

Prevents docking of Ach vesicle on the inner surface of cell membrane

Prevents exocytosis of Ach vesicles
When injected into a striate muscle, paresis occurs after 2 - 5 days.

Duration of effect 2-3 months before it gradually starts to wear off.

When antibodies against BT are formed, the duration of action and the extent of the maximal therapeutic effect are usually reduced.
ACETYLCHOLINESTERASE INHIBITORS

- Increase acetylcholine in NMJ
- Therapeutically used in the treatment of myasthenia gravis
  
  e.g. Neostigmine, edrophonium, pyridostigmine
MYASTHENIA GRAVIS

- Nerve
- Synaptic vesicle
- ACh
- IgG
- C1 complex
- AChR

Activation of the complement cascade leads to formation of the MAC

Destruction of the morphology of the muscle membrane
ACETYLCHOLINESTERASE INHIBITOR

Break down by Acetylcholinesterase
ACETYLCHOLINESTERASE INHIBITORS

Adverse Effects:
- Abdominal cramps
- Diarrhoea
- Excessive salivation
- Lacrimation
- Sweating

These are muscarinic side effects and can be treated by anticholinergic drugs like propantheline without loss of nicotinic effect.