Sugammadex: New Emerging Antidote for Muscle Relaxants

An essay submitted for the partial fulfillment of Master Degree ***in Anesthesia***

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بسم الله الرحمن الرحيم

﴿ قَالُوا سُبْحَانَكَ لا عِلْمَ لَنَا إِلاَّ مَا عَلَّمْتَنَا
إِنَّكَ أَنتَ العَلِيم الحَكِيم ﴾

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Sara Hassan Attia

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List of Abbreviations

ACh	Acetylcholine
AChE	Acetylcholinesterase
AChR	Acetylcholine receptors
AMG	Acceleromyography
APTT	Activated partial thromboplastin time
CDs	Cyclodextrin
CICV	cannot intubate cannot ventilate
CL CR	Creatinine clearance
DBS	Double burst stimulation
DMD	Duchenne Muscular Dystrophy
dTc	d-tubocurarine
ECT	Electrocompulsive therapy
EMG	Electromyography
GABA	Gamma Amino Butyric Acid
HR	Heart rate
HVD	Hypoxic ventilatory response
kDa	kiloDalton
KMG	Kinemyography
MAP	Mean arterial pressure
MEPPs	Miniature end-plate potentials
MG	myasthenia gravis
MMG	Mechanomyography
MuSK	Muscle-specific kinase
mV	milliVolt
nAChRs	Nicotinic acetylcholine receptors

List of Abbreviations (Cont.)

NDMRs	Non depolarizing muscle relaxants
NMB	Neuromuscular blockade
NMBA	Neuromuscular blocking agents
NMBD	Neuromuscular blocking drug
NMJ	Neuromuscular junction
NPPE	Negative Pressure Pulmonary Edema
NRb	Neuregulins
PACU	Post anesthesia care unit
PMG	Phonomyography
PONV	post-operative nausea and vomiting
PT	prothrombin time
PT(INR)	International normalized ratio for PT
PTC	Post-tetanic count
QTc	QT-prolongation
RSI	Rapid Sequence Induction
SC	Schwann cell
SCh	Succinylcholine
SNAP-25	synaptosomal-associated protein-25
SNARE	Soluble N-ethylmaleimide sensitive- factor attachment receptor
SRBA	Selective relaxant binding agent
$t_{1/2\beta}$	Terminal elimination half-life
TIVA	total intra-venous anesthesia
TOF	Train of four

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Introduction

Since the introduction of curare in 1912 to produce surgical relaxation in anesthetized patients, neuromuscular blocking agents (NMBAs) have allowed us to immobilize patients and improve medical and surgical interventions ***(Naguib and Brull, 2009).***

The clinical use of NMBAs in anesthesia has come a long way since then and the practice of anesthesia has witnessed the introduction of many new non-depolarizing neuromuscular blockers that are close to ideal with significant clinical advantages and minimized side effects as compared with older compounds such as d-tubocurarine and pancuronium ***(Raghavendra, 2002).***

Unfortunately, reports of residual post-operative weakness, incomplete recovery and undesired ventilatory effects have continued to appear and no substantial progress has been made in the area of neuromuscular antagonism ***(Naguib, 2007).***

The cholinesterase inhibitor drugs first used to reverse curare currently remain the standard for reversing all NMBAs. The indirect action of cholinesterase inhibitors is

limited in its ability to reverse neuromuscular blockade, and is associated with numerous side effects ***(Welliver et al., 2009).***

Few studies have attempted to explore the potential of non-classic reversal drugs. In this regard, suramin; a P2-purinoceptor antagonist, can reverse non-depolarizing neuromuscular blockade, but it has serious side effects that render it inapplicable for routine clinical use ***(Fields and Vadivelu, 2007).***

A new class of drugs, selective relaxant binding agents (SRBAs), can reverse residual paralysis and has the potential to overcome the limitations of cholinesterase inhibitors. The first SRBA to be introduced is sugammadex. Unlike the cholinesterase inhibitors, which indirectly and competitively antagonize NMBAs by increasing acetylcholine (ACh), sugammadex acts by directly encapsulating, binding, and inactivating NMBAs ***(Welliver et al., 2009).***

Aim of the Essay

This essay is directed towards highlighting the recent class of neuromuscular blockade reversal agent; Sugammadex, and its unique mechanism of action, and to discuss differences between it and the classic neuromuscular blockade reversal agents.

Neuromuscular Transmission

Neuromuscular junction (NMJ) is a refined structure geared to ensure a rapid and efficient transmission of an action potential into depolarization of the postsynaptic target organ, the muscle ***(Hoch, 1999).***

Organization of the neuromuscular junction:

Consideration of the structure and function of the mature NMJ can be conveniently divided into presynaptic, synaptic, and postsynaptic components ***(Hirsch, 2007).***

1. ***Presynaptic Components:***

The motor neuron runs without interruption from the ventral horn of the spinal cord or medulla to the NMJ as a large, myelinated axon. As it approaches the muscle, it branches repeatedly to contact many muscle cells and to gather them into a functional group known as a motor unit. The architecture of the nerve terminal is quite different from that of the rest of the axon. As the terminal reaches the muscle fiber, it loses its myelin to form a spray of terminal branches against the muscle surface and is covered by Schwann cells (SC) **(figure 1)** ***(Martyn et al., 2009).***

Here, the SC anchors the nerve to the muscle membrane. In addition to providing stability and secreting growth and trophic factors, they also participate in axon development and synaptic formation from the fetal state and throughout life. SCs control the number of NMJs and remove superfluous (unnecessary) pre-synaptic nerve terminals, especially during re-innervation, for instance, after crush injury ***(Khirwadkar and Hunter, 2012).***

Both nicotinic and muscarinic receptors are found pre-synaptically on the motor nerve terminal and are involved in modulation of the release of ACh into the NMJ and they have been attributed with both excitatory and inhibitory roles ***(Dand and Lien, 2009).***

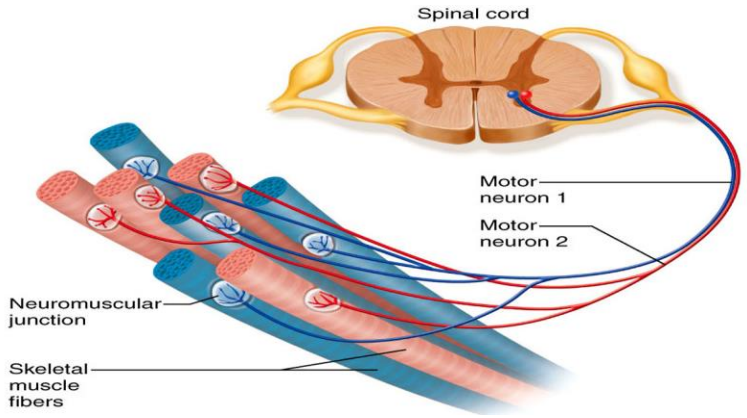

FIGURE 1: The motor nerve originates in the ventral horn of the spinal cord or brainstem. As the nerve approaches its muscle fibers and before attaching itself to the surface of the muscle fiber, the nerve divides into branches that innervate many individual muscle fibers. Each muscle receives only one synapse. The motor nerve loses its myelin and further subdivides into many presynaptic buttons to terminate on the surface of the muscle fiber ***(Martyn, 2015).***

Before fusing with the presynaptic plasma membrane to release the neurotransmitter into the synaptic cleft, synaptic vesicles have to be recruited to and docked at a specialized area of the presynaptic nerve terminal; the active zone. Exocytosis of synaptic vesicles is restricted to the presynaptic active zone, which is characterized by a unique and highly interconnected set of proteins ***(Michel et al., 2015).***

2. ***Synaptic cleft:***

The synaptic cleft measures 50 nm from the motor neuron to the post-synaptic muscle membrane ***(Khirwadkar and Hunter, 2012).***

The nerve and muscle are held in tight alignment by protein filaments called basal lamina, which span the cleft between nerve and end plate ***(Martyn, 2015).***

3. ***Post junctional Components:***

The muscle surface is heavily corrugated, with deep invaginations of the junctional cleft; the primary and secondary clefts, between the folds in the muscle membrane; thus the end plate's total surface area is very large. The depths of the folds also vary between muscle types and species ***(Martyn, 2015).***

On the shoulder of these folds, nAChRs cluster at high density; approximately 5 million of them in each junction and are anchored into the cell membrane by a complex system of cytoskeletal proteins, for example, dystroglycans. AChRs are sparse in the depths between the folds. Instead, these deep areas contain sodium channels **(figure 2)** ***(Cory, 2002).***

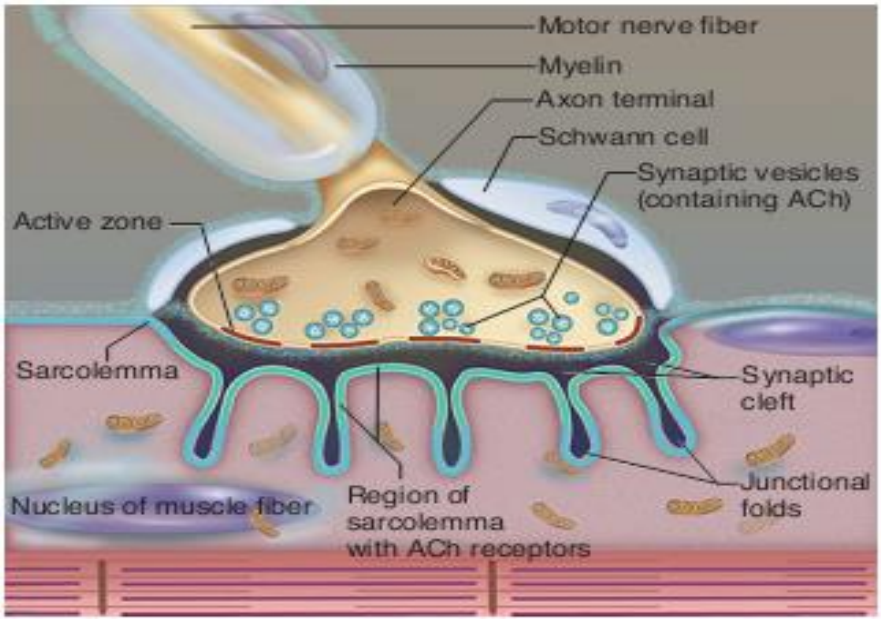

FIGURE 2: Adult neuromuscular junction with the three cells that constitute the synapse: the motor neuron, muscle fiber, and Schewann cell. The motor neuron from the ventral horn of the spinal cord innervates the muscle. Each fiber receives only one synapse. The motor nerve loses its myelin and terminates on the muscle fiber. The nerve terminal, covered by a Schewann cell, has vesicles clustered about the membrane thickenings, which are the active zones, toward its synaptic side and mitochondria and microtubules toward its other side. A synaptic gutter, made up of a primary and many secondary clefts, separates the nerve from the muscle. The muscle surface is corrugated, and dense areas on the shoulders of each fold contain acetylcholine receptors. Sodium channels are present at the cleft and throughout the membrane ***(Miller, 2010).***