ANAESTHETIC MANAGEMENT OF MYASTHENIA GRAVIS

An essay

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presented by

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INTRODUCTION

Myasthenia Gravis (MG) is an autoimmune disease characterized by weakness and fatigability of skeletal muscles, with improvement following rest. It may be localized to specific muscle groups or more generalized. MG is caused by a decrease in the numbers of postsynaptic acetylcholine receptors at the neuromuscular junction, which decreases the capacity of the neuromuscular end-plate to transmit the nerve signal. Initially, in response to a stimulus resulting in depolarization, acetylcholine is released presynaptically which results in a muscle action potential being generated. In MG, the number of activated postsynaptic receptors may be insufficient to trigger a muscle action potential. Further, with repeated stimulation, the decline in release of acetylcholine correlates with the characteristic fatigability ***(Farrugia et al., 2010)***.

MG may be associated with other disorders of autoimmune origin such as thyroid hypofunction, rheumatoid arthritis and systemic lupus erythematosus. The role of the thymus in the pathogenesis of MG is not entirely clear, but 75% of patients with MG have some degree of thymus

abnormality (e.g, hyperplasia in 85% of cases, thymoma in15% of cases). However, the stimulus that initiates the autoimmune process has not been identified ***(Miller, 2005).***

AIM OF THE WORK

The aim of this work is to clarify the pathophysiology, treatment and perioperative anesthetic management of myasthenia gravis to decrease the risk of complications.

PATHOPHYSIOLOGY OF MYASTHENIA GRAVIS

The neuromuscular junction consists of a motor neurone and a muscle cell separated by a narrow synaptic cleft. The nerve and muscle do not come into direct contact. Transmission of the action potential from the nerve to the muscle occurs by release of acetylcholine from the presynaptic nerve terminal ***(Ruff , 2003).***

Motor Neurone :

The motor neurones which control skeletal muscle are long cells which have their origin in the ventral horn of the spinal cord. They extend to muscle cells in the periphery over a distance of up to 1 m . The metabolic centre of the nerve cell is its cell body, which lies near its origin. Information from the cell body is transmitted down a long cylindrical structure known as the axon. Axons are typically 10–20 μm in diameter and are surrounded by a myelin sheath. This sheath serves to increase the speed of transmission of the action potential to the neuromuscular junction. It consists of many layers of cell membrane tightly wrapped around each other acting as an insulator. The myelin sheath is interrupted by gaps (nodes of Ranvier) which participate in the

propagation of the action potential along the nerve, speeding up nerve conduction ***(Standaert, 2000).***

Before the nerve reaches the neuromuscular junction, the axon branches into several terminals to innervate many muscle cells. A muscle cell has only one neuromuscular junction and is innervated by only one nerve. A nerve, and the muscle cells which it innervates, comprise a motor unit. The number of muscle cells per motor unit varies from a few to strong bulky muscles concerned with coarse movement; the smallest number are in muscles which perform delicate movements as the eye ***(Schiavo et al., 2000).***

The synapse is the area of the nerve lying closest to the muscle cell; it is situated opposite a specialised area of the muscle cell called the end plate. The synapse and the end plate are separated by a gap (approximately 20 nm) called the synaptic or junctional cleft which is filled with extracellular fluid. It is at the synapse that the action potential, which has travelled along the nerve, causes the release of the acetylcholine. Acetylcholine travels across the synaptic cleft and binds selectively to the post-synaptic motor end plate of the muscle causing an action potential to travel through it ***(Abbas, 2003).***

Motor End Plate:

The motor end plate is a small, specialised area of muscle which is very rich in acetylcholine receptors. It is oval in shape, measuring 15–30 nm by 20–50 nm. The the end plate is deeply folded with many ridges and secondary clefts. The ridges have a high concentration of acetylcholine receptors on the crest of their folds (Fig. 1). There are 1–10 million receptors at each end plate and the receptor density is high (10,000–20,000 /m–2) ***(Arber et al., 2002).***

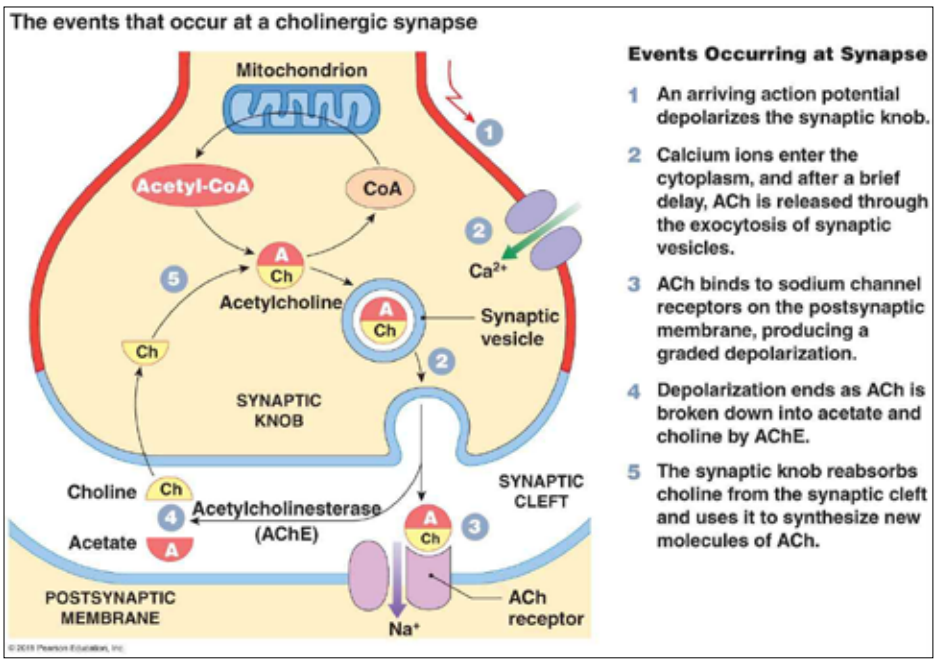

Figure 1: Synthesis, storage and releaseof acetylcholine and its interaction with the post-synaptic nicotinic receptors before being brocken down by cholinesterase.

Synthesis and Storage of Acetylcholine:

Acetylcholine is synthesised from choline and acetyl coenzyme A in the axoplasm of the cholinergic nerve terminals. The reaction is catalysed by the enzyme choline acetyltransferase. Choline acetyltransferase is synthesized in the ribosomes in the cell body of the motor neurone and passes along the axon to its terminal where its concentration is highest ***(Fon et al., 2001).***

The majority of the choline used in acetylcholine synthesis is derived from the extracellular fluid. Most of this choline comes from the diet, although a small amount is synthesised in the liver. About half of the choline formed by the breakdown of acetylcholine at the neuromuscular junction is taken up again into the nerve terminals by a carrier-facilitated transport mechanism before being converted back into acetylcholine ***(Arber et al., 2002).***

Acetylcholine can be found throughout the axoplasm and cytosol of the cell body. Its highest concentration is within the axon terminal. There are different pools or vesicles of acetylcholine in the terminal that have variable availability for release. About 1% of the vesicles form the immediately releasable store which is responsible for the maintenance of transmitter release under conditions of low

nerve activity. Nearly 80% of acetylcholine is in a reserve pool which is released in response to nerve impulses. The remainder is termed the stationary store as shown in (fig.1) ***(Mirakhur et al, 1999).***

Most acetylcholine is stored in vesicles which are synthesised in the cell body and pass down the axon to the nerve terminal by axoplasmic flow. Only about 20% is dissolved in the cytosol. Each vesicle contains approximately 12,000 molecules of acetylcholine. The acetylcholine is loaded into the vesicles by an active transport process in the vesicle membrane involving an Mg2+-dependent proton pumping ATPase. The acetylcholine molecules in the axoplasm combine with a transport protein which shuttles across the vesicle membrane and exchanges each acetylcholine molecule for a H^+ ion ***(Vincent, 2001).***

Release of Acetylcholine:

The release of acetylcholine may be spontaneous or in response to a nerve impulse. There are four modes of spontaneous release–quantal, subquantal, giant and molecular leakage. Random miniature end plate potentials (mepps) of 0.5–1 mV may be detected by an intracellular electrode in the absence of an action potential. These are thought to be

caused by quantal release of acetylcholine. The mechanisms of the four modes of release are:

(1) Quantal release due to exocytosis of one synaptic vesicle.

(2) Subquantal release from exocytosis of an incompletely filled vesicle.

(3) Giant release where a quantity of axoplasm containing acetylcholine is ejected through the membrane.

(4) Non-quantal leakage by diffusion of acetylcholine through the membrane.

(Wood et al., 2001).

When the nerve terminal is invaded by a nerve impulse, Ca2+ channels (P type) in the terminal membrane open, Ca2+ enters the nerve terminal and there is a Ca2+-dependent, synchronous release of the contents of 50–100 vesicles as shown in (Fig.2). To enable the contents of the vesicle to be released, the vesicles must be get a special release sites (active zones) in that part of the terminal axonal membrane which faces the post-junctional acetylcholine receptors. These are the vesicles which form the immediately available store ***(Poage et al., 2002)***.

Once the vesicle contents have been discharged, they are rapidly refilled from the reserve store. The reserve vesicles are anchored to actin fibrils in the cytoskeleton by vesicular proteins called synapsins. Some of the Ca2+ ions that enter the axoplasm on arrival of the nerve impulse bind to calmodulin which then activates an enzyme, protein kinase II. Protein kinase II phosphorylates synapsin which then dissociates from the vesicle, allowing the vesicle to move forward to the release site as shown in (fig. 2) ***(Poage et al., 2002)***.

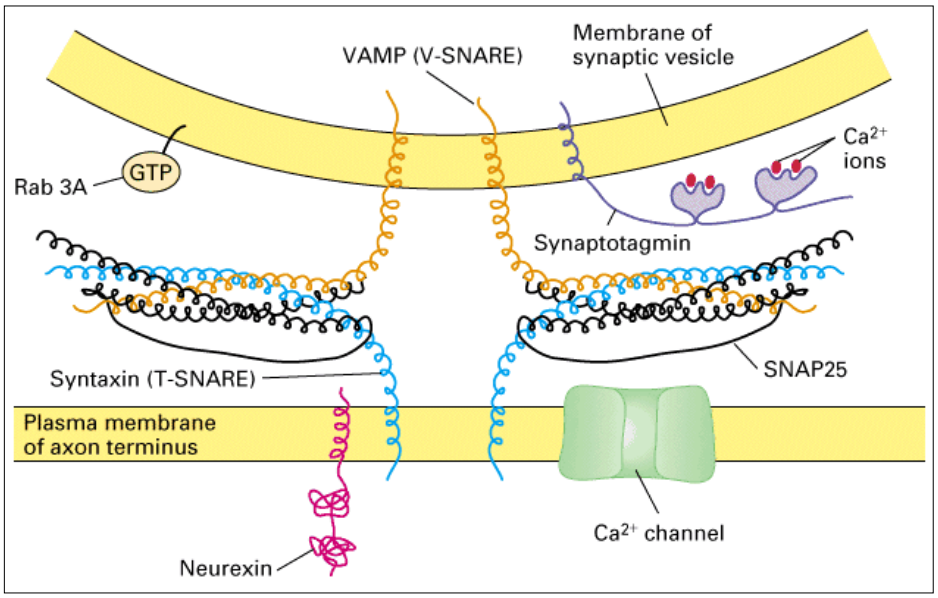

Figure 2: Relationship of the major vesicular proteins concerned with acetylcholine release to the synaptic vesicle membrane (ring-like structure). Synaptophysins, synaptobrevins and synaptotagmin are integral membrane proteins.

The vesicle reach its special sites and subsequent discharge of the vesicular contents involves several proteins. These include the Ca2+ binding proteins synaptotagmin and synaptobrevin (integral vesicle associated membrane proteins (VAMP)), synaptosomal associated protein of 25 kDa (SNAP-25) and syntaxin which are integral terminal axonal membrane proteins present at the active site or release zones. Docking involves an interaction between synaptobrevin, SNAP-25 and syntaxin. In the absence of Ca2+, synaptotagmin functions as a vesicle clamp holding the vesicles in a fusion-ready state but blocking release of their contents. Calcium entry and binding to synaptotagmin activates an ATPase that becomes part of the vesicle active zone complex. Hydrolysis of ATP, together with synaptotagmin binding, leads to exocytosis as shown in (fig. 3) ***(Smit et al., 2001).***

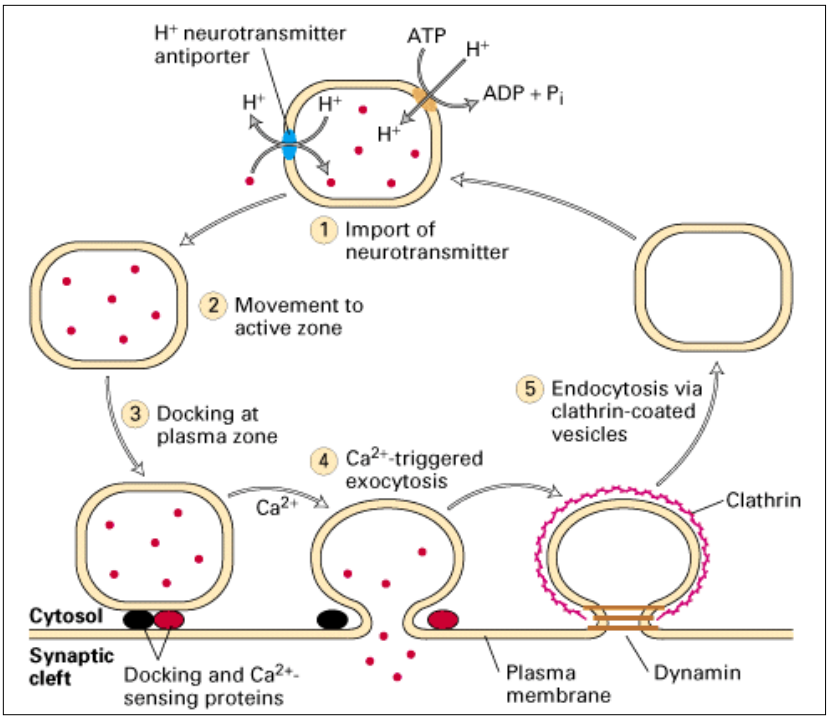

Figure 3: The docking of the vesicle and release of its content.

The acetylcholine receptor:

Acetylcholine receptors in the post-junctional membrane of the motor end plate are of the nicotinic type. The density of acetylcholine receptors at the end plate has been estimated as10,000–20,000 □m2. The high density is facilitated by the presence of junctional folds (Fig. 1). Nicotinic receptors are made up of five protein subunits joined together to form a ring that penetrates through and projects on each side of the membrane (Fig. 3). Each type of protein subunit is specified by a different gene. The subunits

have varying molecular weights and different properties. They are denoted by the Greek letters α, β, γ, δ and ε. There are 9 different α-type subunits (α1–α9), 4 β-subunits and 1 each of the γ, δ and ε units. Therefore, the theoretical number of different nicotinic receptor subtypes is large, but the number is limited in that all receptors contain 2 α-subunits and 1 δ, β and ε unit. In the fetus, γ replaces ε. In addition, there are restrictions on the ability of some α-subunits to pair with others ***(Lee, 2001).***

The receptors are synthesized in muscle cells which make a series of protein subunits and assemble them like barrel staves into cylindrical receptors. Each cylinder crosses from one side of the cell membrane to the other and has a central funnel shaped pore which is an ion channel. The ion channel is 4 nm in diameter at the entrance and narrows to <0.7 nm within the membrane. The receptor complex is 11 nm in length, half of which protrudes from the extracellular surface of the membrane. The protein passes through the membrane but only extends 2 nm into the cytoplasm of the muscle cell. Several proteins have been identified which appear to aggregate the receptors and anchor them to the cytoskeleton. It is thought that agrin is secreted by the motor nerve and triggers localised clustering of the receptors in the end plate. Rapsyn, which is associated with

the inner surface of the postjunctional membrane, links the receptors to the underlying cytoskeleton ***(Kaminski, 2003).***

When two acetylcholine receptors bind to the pentameric complex, they induce a conformational change in the proteins of the α-subunits which opens the channel. At its narrowest, the channel is large enough to let all cations pass through indiscriminately. Potassium ions leak from the inside of the cell to the outside but this movement is minor compared with the movement of Na+ ions from outside to the inside. The inside of the cell is negative with respect to the outside and has a resting membrane potential of –80 mV. Thus, the Na+ ions are attracted to the inside of the cell and make it more positive. This induces a depolarisation or change toward a less negative charge and, once a threshold of –50 mV is reached, voltage-gated sodium channels on the sarcolemma open and allow the flow of Na+ ions into the muscle. This increases the rate of depolarisation, forming an action potential that passes around the whole sarcolemma, causing the muscle to contract ***(Brejc et al., 2001).***

The amount of acetylcholine released following a nerve action potential is far in excess of what is needed to reach the threshold at the end plate. It is estimated that only 6–25% of the acetylcholine normally released is required to reach the threshold potential. The activated acetylcholine