PROLONGED APNEA

RELATED TO ANAESTHESIA

ESSAY

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By

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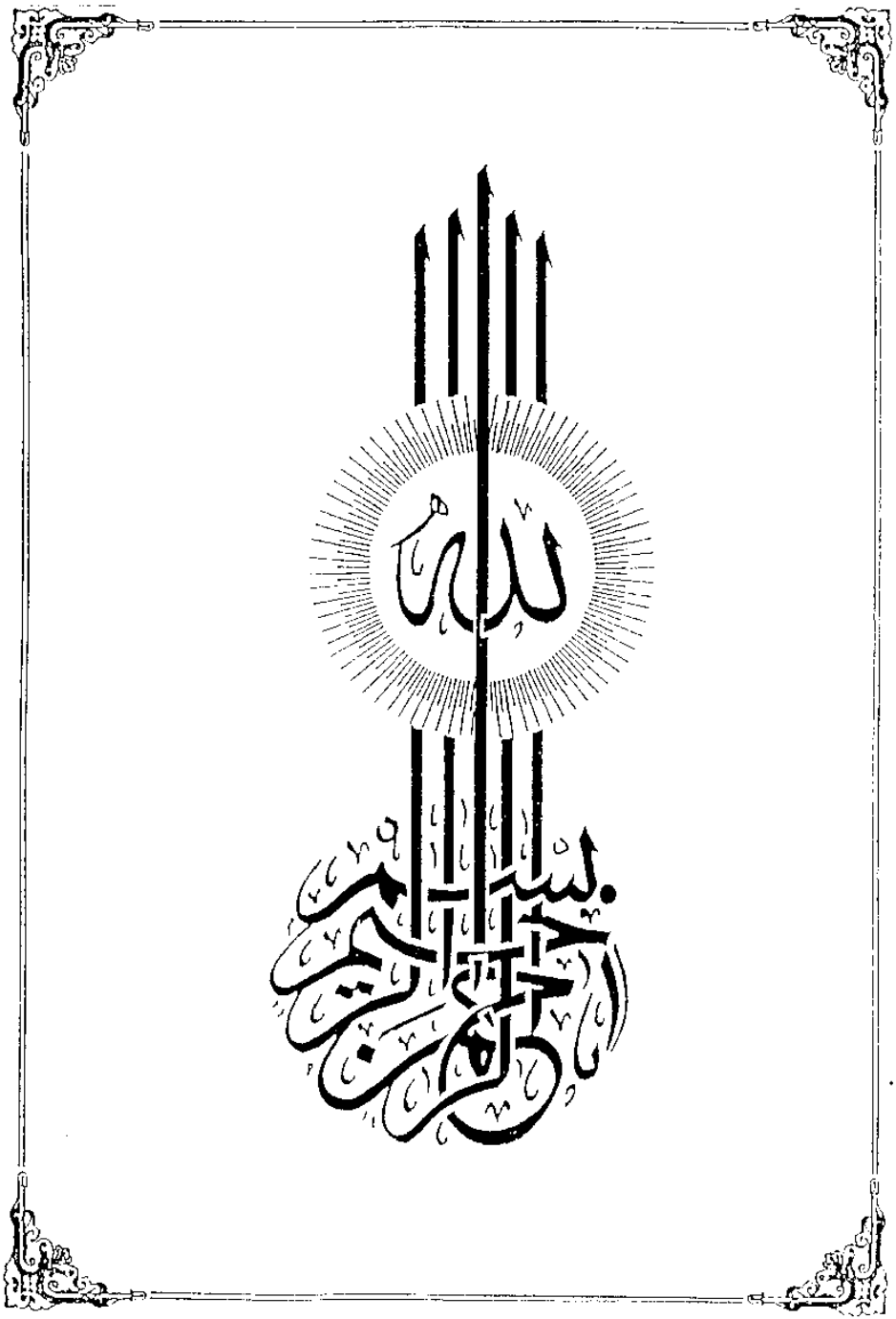

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INTRODUCTION

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It should not be forgotten that our anaesthetic agents and adjuvants are among the most potent and rapidly acting drugs used in medicine. The anaesthetics and techniques have the power to impaire and abolish a variety of essential bodily functions and sometimes leave the patient open to the risk of anaesthetic-related complications .

Apnea may be induced by the anaesthetist for a controlled period during anaesthesia, but if it is prolonged against his desire , it will perform one of the most serious anaesthetic complications. Proper diagnosis of the cause and accurate management of it are essential for success in re-establishment of spontaneous respiration of the patient .

PHYSIOLOGY

NEUROMUSCULAR TRANSMISSION

Anatomy of the neuromuscular junction : (Fig. 1)

As myelinated motor nerve fibre approaches the muscle fibres , it divides into numerous nonmyelinated terminal branches. Each of these branches runs parallel to the axis of the muscle fibres and is embeded in a shallow gutter in the muscle surface (Birks et al., 1960). At the myoneural junction , the nerve terminal is covered by the Schwan cell which forms an anatomical barrier separating the end plate from the extracellular fluid .

The groove between the nerve terminal and muscle fibre is folded inward to make indentations toward the muscle fibre. It is called the junctional folds .

Acetylcholinesterase which destroys the transmitter in the synaptic cleft , is mainly located in the basement membrane and evenly distributed over the whole subsynaptic membrane including the depth of the folds (Dreyer ,1982).

The presynaptic area is characterized by specialized structures , called "active zones ", which are believed to be the release sites of acetylcholine-filled vesicles . These active zones are located just opposite the openings of the junctional folds .

Acetylcholine receptors are sharply localized to the crests of the junctional folds , just beneath the active zones (Daniels and Vogel ,1975) . The acetylcholine receptors have two functions in the physiological chain

of events that lead to the contraction of muscle fibres after nerve stimulation : First , the recognition of the neurotransmitter molecules, and second, the formation of an open ion channel which results in a membrane permeability change .

The ion channel is in a shut, non-conducting conformation in the resting state. After binding of agonist molecules to the recognition sites of the receptor, the agonist-receptor complex changes to an active conformation. This is associated with the opening of the ion channel (Fig. 2) .

The ion channel controles the flow of small cations like Na^+, K^+ , and to a lesser extent , Ca^{++} through the membrane (Dreyer ,1982).

Physiology of neuromuscular transmission :

There is a potential difference between the inside and the outside of the cell. This electromotive force is the result of the semi-permeable property of the cell membrane which permits some ions to traverse the cell barrier more readily than others. Potassium is the most permeable ion in the resting state . So the magnitude of the resting membrane potential and therefore the excitability of nerve and muscle depends upon the ratio of potassium ions inside the cell to those outside it .

The main extracellular ion is sodium. It is only one-fifth as permeable as potassium in the resting state.

Thus it plays a little role in determining the membrane potential.

During electrical activity the cell membrane becomes specifically permeable to sodium. As a result,the cell membrane potential falls. Provided the polarity of the cell membrane reaches a critical threshold level an action potential results. This is the process of depolarization.

In order to restore the transmembrane potential after depolarization the sodium ions that have entered the cell during the initial depolarization must be removed by the sodium pump and potassium equilibriumis restored (Wylie and Churchill-Davidson ,1979).

Acetylcholine Synthesis and Release :

Acetylcholine is formed by acetylation of choline (actively transported across the nerve terminal membrane) by acetyl coenzyme A (from mitochondria) with choline-o-acetyl transferase as a catalyst. While the ultimate source of choline is the plasma , up to 50% of choline which is actively transported into the nerve terminal is derived from the hydrolysis of previously released acetyl choline; moreover , the rate of uptake is increased by nerve stimulation , thus enabling synthesis of acetylcholine to keep pace with the release (Hebb ,1972) .

Acetylcholine exists in the motor nerve ending in three forms: storage acetylcholine ; reserve acetylcholine; and immediately available acetylcholine. Only the

immediately available acetyl choline can be released immediately by each nerve stimulation while the rest acts as a depot (Gray et al.,1980).

The released acetylcholine activates end-plate receptors and is hydrolysed by cholinesterasein the junctional cleft. Some of the produced choline is taken back into the nerve ending and re-synthetised to acetylcholine , the rest diffuses away .

The Role Of Calcium:

An action potential is the normal activator for release of transmitter but this function belongs to a calcium flux initiated by the action potential (Katz and Miledi ,1969b). Neither sodium flux nor depolarization will produce the release of transmitter if calcium is not present. Moreover , the number of quanta released by a stimulated nerve is greatly influenced by the concentration of ionized calcium in the extracellular fluid.

Calcium is presumed to enter the nerve via special proteins that form channels through the nerve membrane. Calcium channels most intimately involved in the release of transmitter are located along the active zones . These channels are opened by the action potential , either directly or by cyclic AMP formed during the action potential (Standaert and Dretchen ,1981).

The presence of the ion in the area of the active zone seems to initiate a process in which the vesicle membrane fuses with the cell membrane and thereby connects the interior of the vesicle to the extracellular space of the junctional cleft. Transmitter leaves the opened vesicle and crosses the junctional cleft to react with cholinoreceptors or be destroyed by cholinesterase or both (Standaert ,1982).

Effect Of Magnesium On Transmission Release :

Magnesium blocks the transmission, propably by interfering with the presynaptic release of acetylcholine. If given in increasing quantities, magnesium finally produces complete blockade. Similarly , withdrawal of calcium produce the same effect and these two ions appear to be antagonistic (Wylie and Churchill Davidson, 1979).

Margin Of Safety Of Neuromuscular Transmission :

In normal patient there is a large margin of safety in neuromuscular transmission. Paton and Waud (1967) indicated that it was possible for the system to function in response to stimulation even though over 70% of the receptors on the post-synaptic membrane were blocked by curare. In other words, over 70% of the cholinergic receptors needed to be occupied before

any signs of paresis took place. Some skeletal muscles require a higher percentage of receptor occupancy than others before signs of paresis are evident. For example, it has been suggested that the diaphragm requires 90% occupancy before its function starts to fail. It is important to realise that a patient may appear to have completely recovered from the effect of relaxant drugs and yet have a greatly reduced margin of safety of neuromuscular transmission (Wylie and Churchill-Davidson, 1979).

TYPES OF NEUROMUSCULAR BLOCK :

Two principal groups of drugs are used clinically to produce neuromuscular block the so called depolarizing and non depolarizing neuromuscular blocking agents .

1. Nondepolarization Block : (Fig. 3a)

The molecules of the blocking agent compete with acetylcholine for the receptor sites on the post-junctional membrane. The activity of the drug depends on its concentration at the end-plate relative to acetylcholine concentration. Therefore , any condition that increases the release of acetylcholine or prevents its destruction e.g. anticholinesterase, will increase acetyl choline concentration relative to the blocking drug reversing its activity. In other words, the degree of neuromuscular block is directly proportional to the concentration

of the drug and inversely to the acetylcholine concentration. It was suggested that a curare-like drug forms a union with the receptor and the energy value of this union depends upon the molecular configuration of the drug and so will determine its duration of action.

Acetylcholine and other depolarizing drugs can actively remove the drug from the receptor and break the union between them .

The assumption that neuromuscular blocking agents acts only on the postsynaptic membrane, has been challenged by Riker and Okamoto in 1969. The presynaptic activity of nondepolarizing drugs was considered for d-tubocurarine, dimethylcurarine and pancuronium. This presynaptic action affects the dynamics of transmitter mobilisation from reserve stores. Curare and gallamine undoubtly have some action on the presynaptic nerve endings (Hubbard and Wilson ,1973).

Characters Of Nondepolarizing Blockers :

(1) They don't cause muscular fasciculation on intravenous injection nor post-operative muscle pains.

(2) Their effects are decreased by anticholinesterase, acetylcholine, depolarizing relaxants and on repeated tetanic stimulation .

(3) Paralysis is increased by nondepolarizing agents , ether, halothane, enflurane and severe hypothermia (below 30 C°) (Atkinson et al., 1982).

II. Depolarization Block :

Depolarizing drugs cause lowering of the transmembrane potential of the postsynaptic membrane to a level that prevent the triggering of a propagated action potential by acetylcholine. Lowering of the resting membrane potential from-90 to -57 renders it refractory to stimulation . Katz and Thesleff (1957) found, however, that the duration of depolarization was very much shorter than the duration of insensitivity of the membrane to acetylcholine. Even after the potential of the post synaptic membrane of the muscle had once again returned to its normal value, the muscle remained unresponsive to acetylcholine. This phase of neuromuscular block is termed by them , the desensitizing phase of depolarizing neuromuscular block (Fig.3b) .

The presynaptic action of depolarizing drugs was suggested by Galindo (1971), and blamed as a cause for another type of block called phase II block .

Unlike nondepolarizing relaxants, depolarizing drugs are not bound to the receptor site for a long duration (Feldman and Tyrell ,1970).