The physiology of neuromuscular transmission

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The Physiology of Neuromuscular Transmission

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There are few instances in which the elucidation of a physiological mechanism has been so dependent upon pharmacological experiments as in the case of neuromuscular transmission. Evidence for this, no doubt, will be forthcoming during the symposium, and we are likely to have many opportunities for a discussion of the actions of curare in relation to the transmission process. In this presentation I will limit myself to a brief outline of the main events in synaptic transmission with emphasis only on a few of those steps which are relevant to the action of curare.

The most important events of neuromuscular transmission are schematically shown in Fig. 1. For anatomical as well as functional reasons it seems

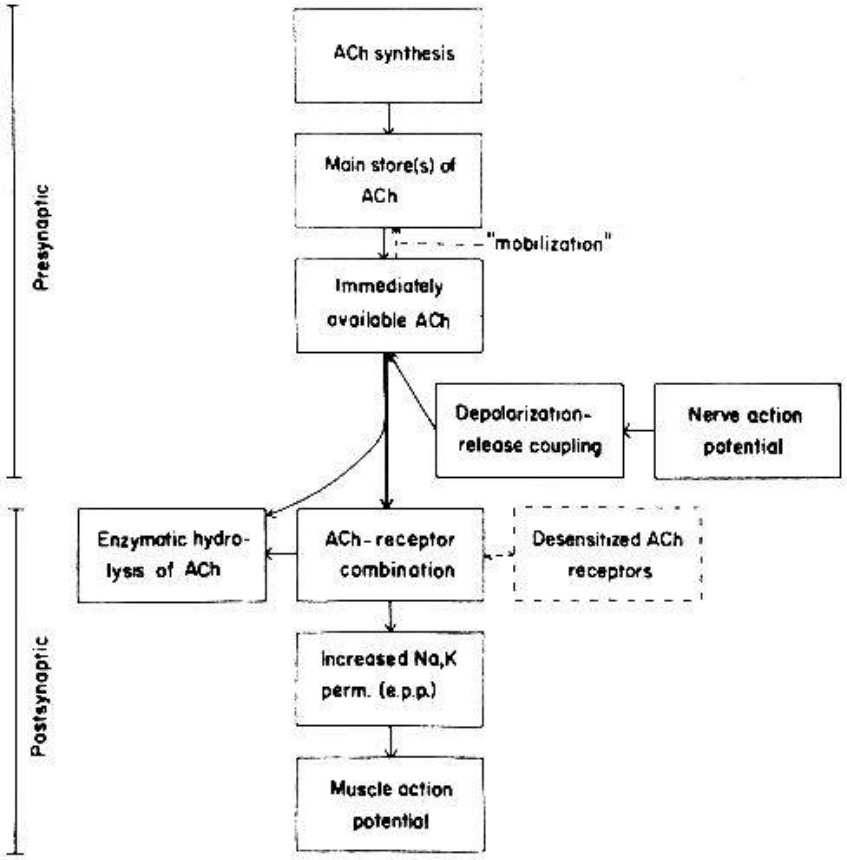

Fig. 1. A diagram showing the main steps involved in neuromuscular transmission (Thesleff and Quastel 1965).

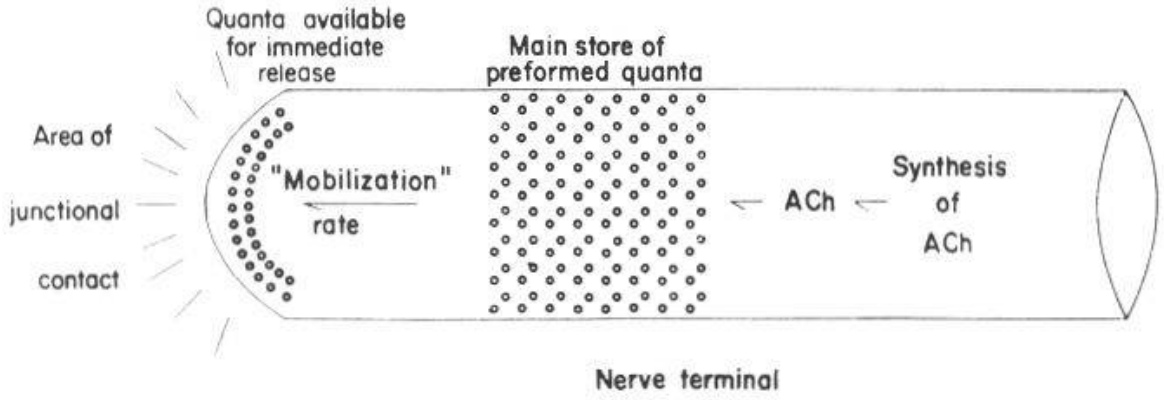

Fig. 2. A hypothetical model showing the storage sites for acetylcholine in a motor nerve terminal.

appropriate to divide them into those involving either the presynaptic or the postsynaptic part of the junction.

The presynaptic part consists of the synthesis and storage of acetylcholine and the subsequent release of the transmitter through the mediation of the nerve action potential and a depolarization-release coupling mechanism.

The nerve terminal contains transmitter sufficient for several thousands of impulses, the transmitter being stored in an inactive form, presumably within submicroscopic vesicles as multimolecular quanta or packets of acetylcholine. It has been estimated that in a human motor nerve each ending contains a total of about 200 000 quanta of acetylcholine (ELMQVIST and QUASTEL 1965). Of this main storage pool, however, only a small fraction is available for immediate release by a nerve impulse as shown in a hypothetical model (Fig. 2). During repetitive nerve stimulation it is the size of this readily releasable fraction and the rate at which transmitter is «mobilized» into that pool that are the main determinants of the amount of transmitter liberated by each nerve impulse. For instance early tetanic rundown, i.e. the rapid decrease in the amount of transmitter released during high frequency nerve stimulation, is due to the depletion of the readily available store of transmitter. This is illustrated in Fig. 3 which

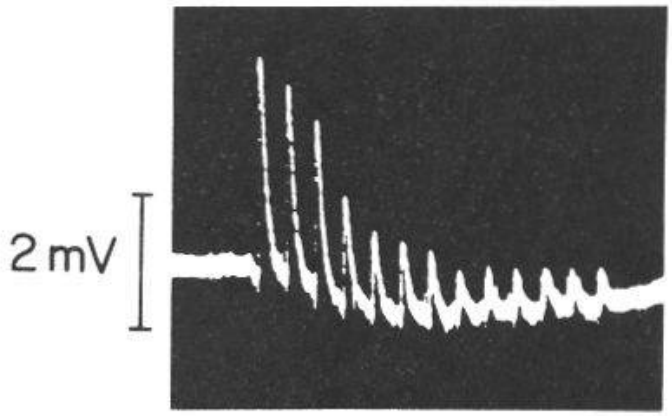

Fig. 3. Sequential end plate potentials in a partly curarized human muscle fibre stimulated through its nerve at 100/sec (DAHLBÄCK et al. 1961).

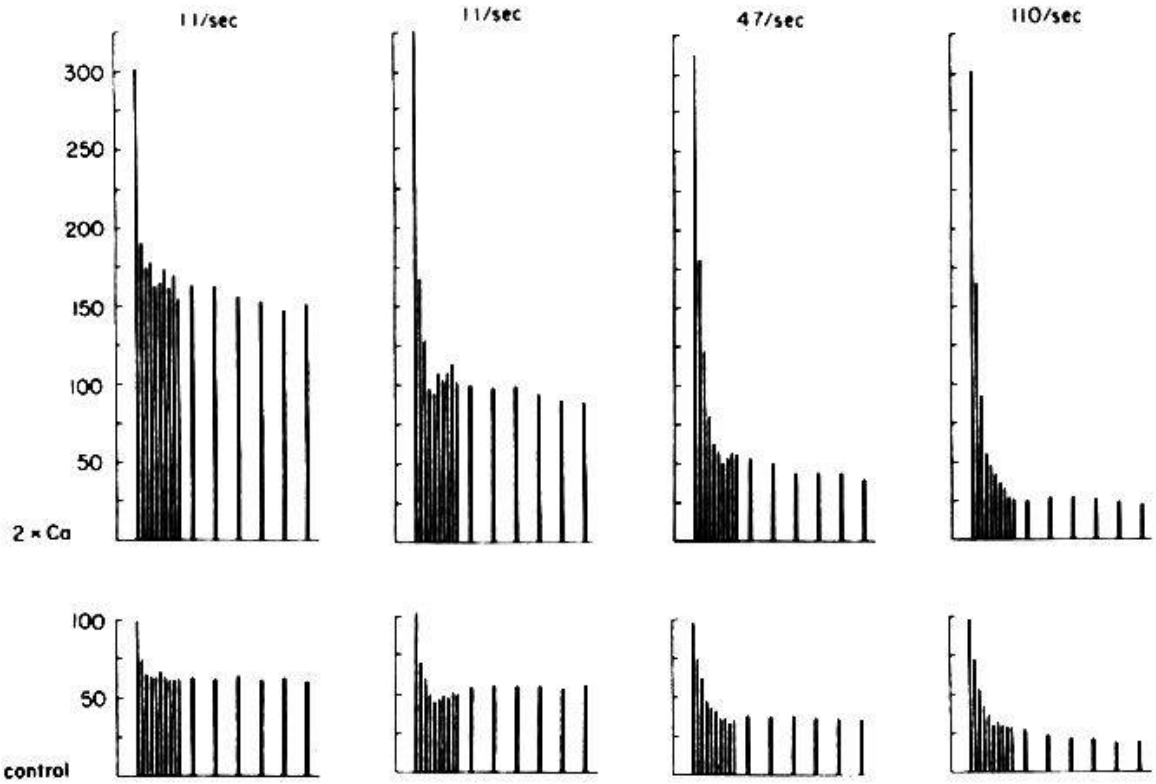

Fig. 4. Number of quanta contained in end plate potentials of partially curarized human muscle fibres during tetani 40 impulses long at four different frequencies of stimulation in normal bathing solution and after doubling the Ca^{++} concentration. The first ten bars represent averages of five sequential end plate potentials (ELMQVIST and QUASTEL 1965).

shows sequential end plate potentials in a curarized human muscle fibre during nerve stimulation at 100/sec. The fall in amplitude of the end plate potential is due to a reduction in the number of quanta released by each impulse, i.e. it is attributable to a partial depletion of the part of the transmitter store that is available for immediate release. The plateau at which end plate potentials levels off marks the point when an equilibrium has been reached between the amount of transmitter liberated per unit time and the rate at which transmitter is replenished from the main store to become available for release.

Another factor of importance for transmitter release is the calcium ion concentration. As shown in elegant experiments (CASTILLO and KATZ 1954 a, b; KATZ and MILEDI 1965 a) calcium is a necessary co-factor for acetylcholine release by a nerve impulse. The exact place of calcium action in the process of the depolarization-release coupling is, however, unknown. In Fig. 4 are shown the effects of doubling the external concentration of calcium on the number of quanta in end plate potentials during indirect tetanic stimulation of human muscle fibres. In 4 mM calcium the first end plate potential in each tetanus averages three times that in the controls. However, subsequently the end plate potentials decline in amplitude more rapidly than in normal solution. The effect of calcium is to increase the fraction of

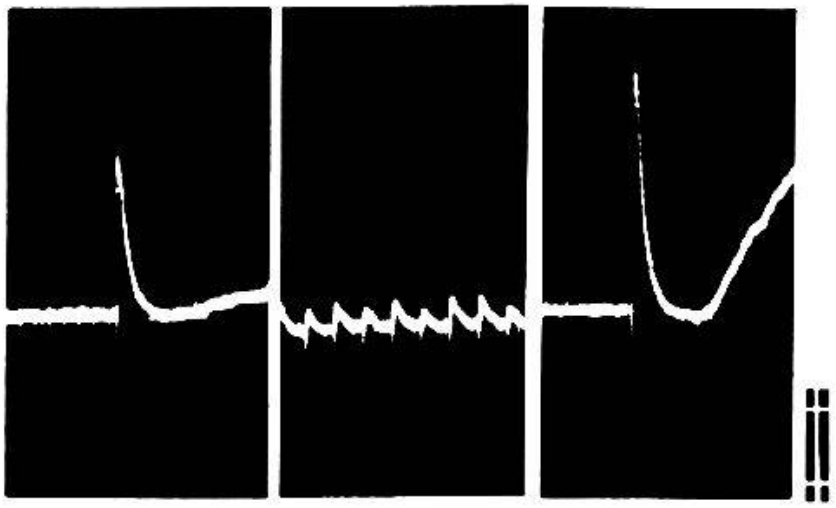

Fig. 5. End plate potentials before (left-hand record), during (middle record) and 10 sec after (right-hand record) a period of repetitive nerve stimulation at about 100/sec in a partially curarized human muscle fibre. Voltage calibration 1 mV (DAHLBÄCK et al. 1961).

the transmitter in the immediately available store that is released by a nerve impulse and this offers an explanation for the high quantum content of the first end plate potential in the train. As already mentioned the fall in amplitude of sequential end plate potentials is attributed to depletion of the presynaptic store of immediately available transmitter. On this basis the size of the end plate potential reflects the amount of transmitter previously released from the store and consequently the amplitude of successive potentials can be expected to fall more rapidly in the presence of high calcium concentrations.

Post-tetanic potentiation, i.e. the period following a high frequency stimulation during which the amount of acetylcholine released by a single nerve impulse is augmented, has recently been suggested to be mediated by a mechanism analogous to the effect of extra calcium (KATZ and MILEDI 1965 a). Fig. 5 shows this phenomenon at a curarized human neuromuscular junction.

HUBBARD and SCHMIDT (1963) have suggested that facilitation of transmitter release may be due to mobilization of quanta inside the terminals, making more of them available for liberation by the next nerve impulse. An alternative possibility would be to attribute post-tetanic potentiation to an increased efficacy of the depolarization-release coupling mechanism possibly mediated by an accumulation of calcium ions released from tissue stores during the preceeding period of nerve stimulation.

Summarizing it can be said that at least three main factors regulate the amount of acetylcholine liberated during repetitive nerve activity: 1. the amount of transmitter in the nerve terminal available for immediate release, 2. the fraction of this amount which is released by the nerve impulse, 3. the extent to which replenishment of transmitter is able to keep up with release.

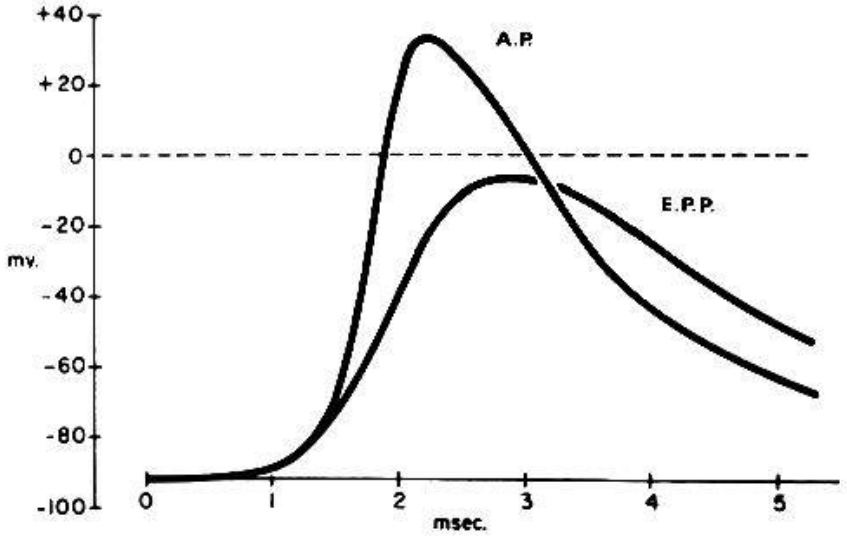

Fig. 6. A schematic drawing showing the approximate time courses and amplitudes of the end plate potential (E.P.P.) and the action potential (A.P.) in a normal muscle fibre.

Following release the transmitter reaches the post-synaptic membrane. In the membrane acetylcholine may combine either with its receptor molecule or with the enzyme cholinesterase. A combination with the latter causes its hydrolysis and inactivation. The acetylcholine receptor reaction brings about, as shown by TAKEUCHI and TAKEUCHI (1960), a localized and simultaneous increase in the membrane permeability to sodium and potassium ions. This is equivalent to a shunt of the electrical resistance of the membrane and the end plate region of the muscle fibre is therefore depolarized according to the electrochemical driving forces of the two ions involved. When the end plate potential is large enough the membrane potential difference triggers a self-regenerating action potential involving selective and in time separate membrane permeability changes to sodium and potassium ions.

Fig. 6 is a schematic drawing showing the end plate potential and the action potential as separate events. It is evident that the end plate potential is much bigger than is necessary for triggering the action potential, i.e. there is a large safety margin for neuromuscular transmission. On the other hand when curare is present and reduces the sensitivity of chemoreceptors the amplitude of the end plate potential may become reduced to a little above or below fibre threshold. Under such conditions transmission is highly sensitive to changes in the amount of acetylcholine released, cholinesterase activity and fibre threshold. Therefore, a number of physiological events and drugs which affect these parameters have little or no observable effect on normal transmission but they drastically change the number of transmitting synapses in a partially curarized muscle.

The mechanism responsible for the end plate potential and that causing the action potential are fundamentally different and as repeatedly stressed by GRUNDFEST, one must assume that separate membrane components are implicated in the generation of the two types of membrane responses. This

assumption has recently found strong support from the observation that tetrodotoxin, a poison of the puffer fish, blocks the sodium conductance of the spike mechanism but has no effect whatsoever on the sodium permeability increase induced by the transmitter (ELMQVIST and FELDMAN 1965; KATZ and MILEDI 1965 b). We have little idea as to the chemical nature of the membrane structures underlying the two types of electrogenesis in muscle and at present this lack of knowledge must be considered the most serious limitation to our understanding of the transmission process and the action of curare upon it.

Summary

Studies of transmitter liberation from motor nerve terminals during repetitive stimulation suggest the following events governing release:

1. The storage pool from which acetylcholine is available for immediate release is small and sufficient only for a few impulses.

2. The fraction of transmitter from this pool which is released by a nerve impulse is determined by previous activity and by the calcium ion concentration.

3. The rate at which transmitter release can continue during repetitive stimulation, is governed by the rate at which transmitter is made available for release by "mobilization" from more distant storage pools.

Zusammenfassung

Studien über die Freisetzung von Transmitter im Gebiet der motorischen Nervenendigungen im Laufe wiederholter Reizung lassen die folgenden, die Ausschüttung steuernden Faktoren vermuten:

1. Nur ein kleiner Vorrat an Acetylcholin steht für die sofortige Freigabe zur Verfügung. Er reicht nur für wenige Impulse aus.

2. Die Fraktion des aus diesem Vorrat durch einen Nervenimpuls freigesetzten Transmitters wird durch die vorangehende Aktivität und durch die Calcium-Ionen-Konzentration bestimmt.

3. Die Geschwindigkeit, mit welcher die Freisetzung des Transmitters im Laufe wiederholter Stimulation erfolgen kann, hängt von der Schnelligkeit der Mobilisierung von Transmitter aus weiter entfernt liegenden Vorratsquellen ab.

Résumé

Des études, portant sur la libération du médiateur chimique au niveau des terminaisons des nerfs moteurs au cours de stimulations itératives, laissent supposer les mécanismes suivants à la base de cette libération:

1. Une faible réserve d'acétylcholine est disponible pour une libération immédiate, cette réserve est juste suffisante pour quelques stimulations.

2. La fraction du médiateur libérée à partir de cette réserve par une stimulation nerveuse est déterminée par l'activité préalable et par la concentration des ions calcium.

3. La vitesse, à laquelle la libération du médiateur peut se poursuivre au cours de la stimulation itérative, dépend de la «mobilisation» du médiateur provenant de réserves plus distantes du lieu de libération.

Riassunto

Degli studi riguardanti la liberazione del mediatore chimico al livello dei fili terminali dei nervi motori durante stimolazione stereotipica, lasciano supporre che i seguenti meccanismi siano alla base di tale liberazione:

1. Una piccola riserva d'acetilcolina è disponibile per ottenere una liberazione immediata. Questa riserva basta però appena per qualche stimolo.

2. La frazione del mediatore chimico liberata da questa riserva mediante stimolazione nervosa, viene determinata dall'attività preliminare e dalla concentrazione degli ioni di calcio.

3. La velocità con cui si può effettuare la liberazione del mediatore durante la stimolazione iterativa, dipende dalla «mobilizzazione» del mediatore che proviene dalle riserve più lontane dal luogo di liberazione.

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