QUANTAL SQUANDER

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The myoneural junction is the region where the nerve terminal meets modified muscle cell membrane. At this site of filamentous branching of the nerve the fibres lose their myelin covering and then spread along the muscle fibre in both directions. The terminal portions of the nerve expand in a club-like fashion, fitting so that they are almost completely embedded into a highly specialized and adapted region of the muscle cell membrane. Though embedded, the structures are not fused, being separated by a narrow cleft. In the region of this synaptic cleft the muscle membrane forms numerous folds, the cleft itself varying between 200 and 500Å in depth. Within this space exists a layer of dense material known as axoplasmic membrane, which is faithfully separated from the membranes of both nerve and muscle by a clear zone.[1] It is across this zone that the chemical transmitting agents released from the nerve terminals on depolarization must pass. At the myoneural junction the chemical transmitting agent has been identified as acetylcholine.[2]

Acetylcholine is produced in the motor neurone and travels to the nerve ending, where it is stored in an inactive state in the form of droplets or vesicles. Constant quanta of acetylcholine are released, apparently at random, from the nerve terminals and produce miniature end-plate potentials.[3] The quantal content of acetylcholine is of the order of 10^4 molecules, and release is a specialized function of the nerve terminal, being independent of any stimulation from the more proximal part of the nerve. These miniature end-plate potentials remain localized to the postsynaptic membrane. The rate of release of acetylcholine is increased by depolarization of the presynaptic membrane and inhibited by its hyperpolarization.[4]

Depolarization of the nerve, as occurs in response to a voluntary impulse, results in an enormous increase in quantal release, so that the end-plate potentials reach threshold level and the muscle cell membrane is depolarized.

The physiology of the myoneural junction is one of the best understood regions of the nervous system. Aspects of the specific and independent function of the nerve endings have been referred to and it is considered reasonable to anticipate that sooner or later a clinical syndrome related to a disordered quantal release will be found. The hypothesis of this paper is that the cases I described in 1961 and 1962 under the title 'A syndrome of continuous muscle-fibre activity'[5, 6] represent an abnormality of the quantal release process.

Clinical Features

The salient symptom of the disease in question was the progressive development of muscle stiffness in previously healthy individuals. The onset was insidious, the muscles becoming more and more difficult to move. The distal muscles suffered most, though proximal muscles were also severely affected. The muscles of mastication, deglutition and respiration suffered least, though respiratory embarrassment was caused on a few occasions by extreme stiffness of chest muscles and diaphragm. The muscle stiffness was curious in that after repeated contraction the degree of mobility improved though it remained grossly abnormal.

Fig. 1. Typical posture.

With continuous movement the improvement was noted to be short lived, because the stiffness recurred in a phasic fashion. There was no familial history of nerve or muscle disorder, the condition was unaffected by the environmental temperature and persisted during sleep. Gradually the more powerful muscles pulled the upper limbs into a state of semiflexion and the feet into persistent cavus. There was no interference with micturition or defaecation. The muscles were firm to the touch, as though in a state of persistent contraction, and in all muscles fasciculation was evident. The persistent stiffness was aggravated considerably by non-repetitive voluntary movement, and the more powerful the effort the greater was the disability; with repetition the condition improved for a while. The abnormality was confined to the motor system, there being no complaint of pain, paraesthesia, or loss of sensation. The tendon reflexes were unobtainable owing to the state of immobility, while plantar stimulation elicited a slow but otherwise normal response. Fig. 1 illustrates the typical posture of this disease.

Retardation of growth in one case and loss of weight in the other were marked features. Both patients perspired profusely and the body temperatures were slightly elevated.

Investigations

Investigations confirmed the state of hypermetabolism, with BMRs varying between +65 and +84. Independently determined oxygen uptakes were markedly elevated, even up to 360 ml./min. under basal conditions. Extensive studies failed to reveal any dysfunction of the endocrine system. Histological examination of the affected muscle revealed little—merely a few disintegrating fibres scattered sparsely in apparently normal muscle tissue.

Electromyography was most informative and showed a rapid discoordinated discharge of independent muscle fibres of bizarre character. This discharge persisted at rest and was aggravated by voluntary contraction. After a prolonged strenuous contraction there occurred a curious electrically silent period lasting for 10 - 20 seconds before the spontaneous return of activity; this silent period could be cut short by voluntary effort at any stage. It is not to be

confused with the silent period noted by Denny-Brown (1928)[7] following upon a phasic myotatic response in muscle to which passive tension was already constantly applied.

Response to Possible Therapeutic Agents

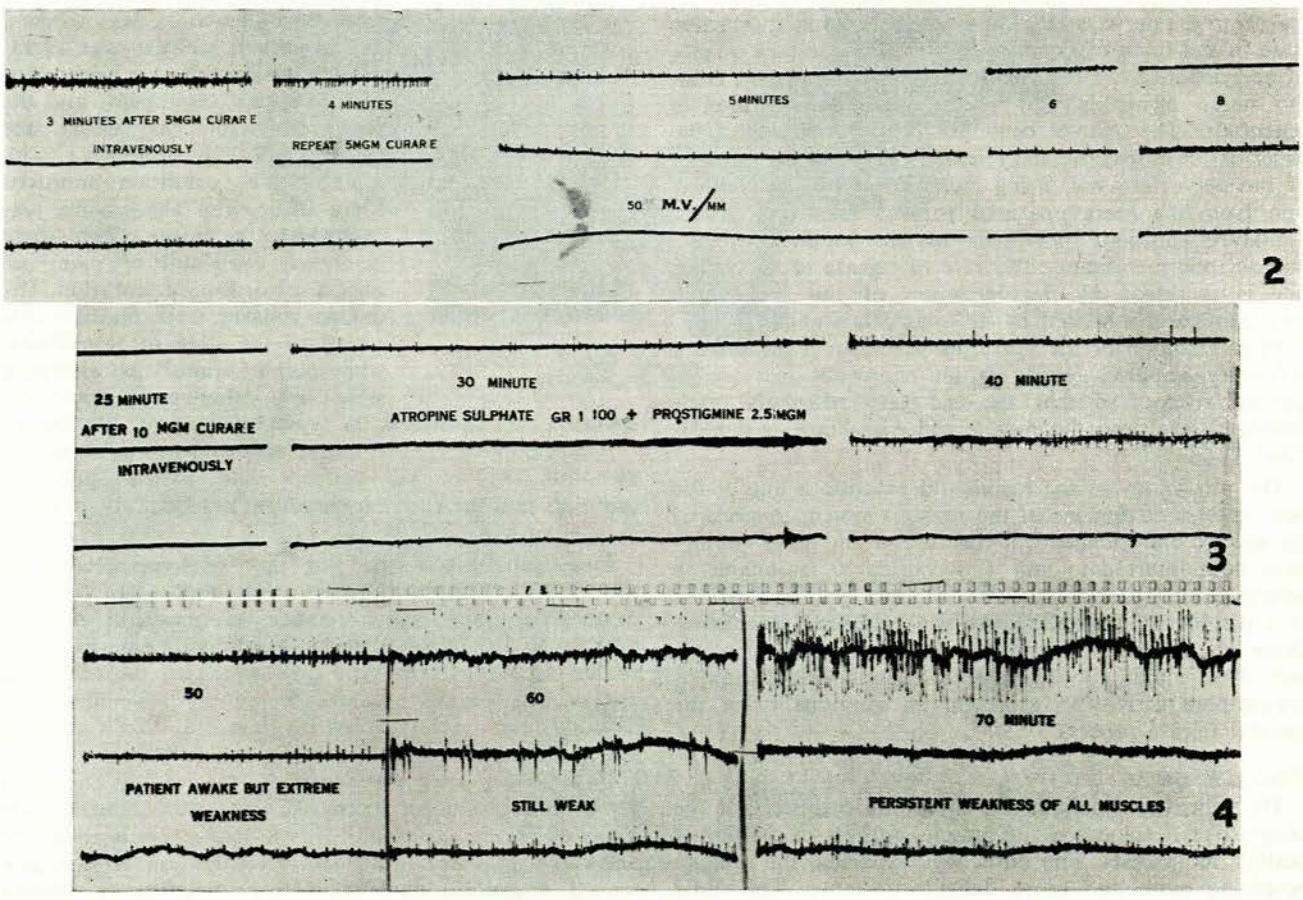
Extensive metabolic studies failed to reveal any abnormality. Electrolyte juggling, hormonal alteration, and remedies to the envy of the spagirist of old, were of no avail.

No significant alteration in the state of persistent contraction followed upon the administration of atropine or prostigmine pushed to uncomfortable levels. Local procaine into the muscle abolished, as it must, the local activity. Nerve blockade producing total sensory and motor inhibition had little effect. Depolarizing agents such as succinylcholine abolished the activity, confirming that the activity was not arising spontaneously from the muscle fibres. Full doses of succinylcholine were required to effect depolarization. A marked sensitivity to the blocking action of curare was found, with disappearance of the abnormal activity; a dose of 1 mg. in the adult case produced muscular weakness and a further 1 mg. produced difficulty with deglutition, phonation and respiration, which lasted well up to 1 hour. Figs. 2-4 demonstrate the changes in spontaneous activity as recorded electromyographically following upon the administration of curare in bigger dosage.

The spontaneous discharges of the nerve terminals were likened finally to the spontaneous central discharge seen in epilepsy. The barbiturates and their derivatives were used and failed. Sodium hydantoinate produced a dramatic recovery within 3 days; the muscles relaxed, fasciculation diminished, and signs of hypermetabolism disappeared. This treatment has been effective in both cases over the past 4 years. The child is back at school and rides there on his bicycle; he has grown considerably, though he is still well below the average build, and his secondary sex characteristics are slow in developing. The adult patient is back at work as a miner, and says he has never felt so well. Both cases are controlled on sodium hydantoinate gr. $1\frac{1}{2}$ *t.d.s.*

Discussion

Little is known about the effect of hydantoinate on acetylcholine and nothing about its effect on acetylcholine release. It is at the level of the presynaptic membrane that hydantoinate seems to function, presumably by decreasing the permeability to acetylcholine directly, or indirectly by altering the permeability to various ions and in particular



Figs. 2-4 demonstrate three electromyographical tracings recording (from above downwards) the activity in the 1st dorsal interosseous, extensor communis, and flexor profundus muscles. The time sequences are marked. In Fig. 4 note the return of spontaneous activity, particularly in the 1st dorsal interosseous muscle at 70 minutes.

sodium. That hydantoinates increase the turnover of sodium ions across the membrane was shown by Woodbury *et al.*[8] in 1958.

It is clear that the spontaneous activity is not due to increased sensitivity of the postsynaptic membrane, for this would be incompatible with the responses obtained with curare and succinylcholine. That the acetylcholine-esterase-acetylase mechanism is normal, is once again inferred from the above and confirmed by the lack of alterations in spontaneous activity during the administration of quinine, prostigmine or atropine.

Summary

Aspects of 2 cases with continuous muscle-fibre activity are discussed. The abnormality has previously been located in the motor-nerve terminals at the myoneural junction. The fault appears to lie with the acetylcholine quantal release mechanism in the form of defective binding or inactivation in the nerve terminals or of undue permeability of the presynaptic membrane itself.

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