DENERVATION SUPERSENSITIVITY: 
THE RESPONSE TO DEPOLARIZING MUSCLE RELAXANTS

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SUMMARY

A case of localized muscular rigidity following suxamethonium is reported in a patient with a lesion involving the brachial plexus. It is suggested that this is an example of contracture, attributable to an acetylcholine partial agonist acting on an enlarged receptor area in the muscle. Other examples of supersensitivity in man are mentioned.

The chemical theory of neuromuscular transmission (Dale, Feldberg and Vogt, 1936) is now almost universally accepted, and implicates acetylcholine as the neuromuscular transmitter. Depolarizing muscle relaxants act, at least initially, in a manner similar to acetylcholine and are believed to produce their effects by prolonged depolarization, but in certain situations these agents, instead of producing muscular paralysis, cause an increase in muscle tension. One such situation is seen with denervated muscle.

That contracture can occur in denervated and partially denervated muscles following acetylcholine and acetylcholine-like substances has been known to the physiologist for a long time (Dale and Gasser, 1926). Reports of this occurrence, however, during anaesthesia are scarce (Marshall, 1964; Wylie and Churchill Davidson, 1972) and the mechanism is obscure.

CASE HISTORY

A 67-year-old man was admitted to hospital for investigation following an 8-week history of pain, paraesthesia, numbness, weakness and swelling of his right arm. Clinical examination revealed dilated veins over his right arm, anterior chest wall and neck. Several hard nodes were palpated in the right supraclavicular fossa. There was weakness and wasting in almost all the muscles of the right arm and forearm, particularly those supplied by C5 and C6 and diminution of sensation over the area supplied by C5, C6, C7 and C8. Horner's syndrome was not present.

A clinical diagnosis of carcinoma of the apex of the lung (Pancoast syndrome) was made, but chest X-ray and tomography were inconclusive. A phlebogram showed occlusion of the axillary vein with a considerable number of collateral venous channels, and a suspicion of a soft tissue mass high in the axilla. It was decided to take a biopsy from the right supraclavicular lymph nodes under general anaesthesia.

After premedication with pethidine 50 mg and promethazine 50 mg, anaesthesia was induced with 2.5% thiopentone 250 mg followed by suxamethonium 50 mg. The vocal cords were sprayed with 4 ml of 4% lignocaine solution and intubation performed. Anaesthesia was maintained with nitrous oxide, oxygen and halothane.

The patient's trunk and limbs had been covered by a blanket up until this stage, and nothing abnormal had been noticed.

The surgeon wished to turn the patient's head to the left to gain access to the right supraclavicular fossa; the neck muscles were clearly not relaxed and attempted movement of the head caused "bucking" on the endotracheal tube. A further 30-mg dose of suxamethonium resulted in fasciculation over most of the body except for the right arm, which became rigid as the rest of the body relaxed. It proved impossible to move the right arm with ordinary force; the rigidity gradually passed off within 3-4 minutes and at the same time muscle power returned in the rest of the body. Biopsy revealed an anaplastic carcinoma infiltrating local structures.

DISCUSSION

Patients with Pancoast syndrome commonly present with pain down the arm, caused mainly by invasion and compression of the lower roots of the brachial plexus. C8, T1, T2 are most often involved. The degree of damage to the nerve fibres will vary considerably, but the end-result in the more severely damaged fibres will be the same, namely Wallerian degeneration of the distal part of the nerve, and degeneration of its terminal motor or sensory end-organ.

It has been known for many years that organs chronically deprived of their innervation show an increased sensitivity to their chemical transmitter. Cannon (1939) thus stated his law of denervation: "when in a series of efferent neurones a unit is destroyed, an irritability to chemical agents develops in the isolated structure, or structures, the effect being maximal in the part directly denervated". Not only do denervated structures become more responsive to chemical transmitters which are their natural stimulants, but to other chemical agents as well.

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(Frank et al., 1923; Von Euler and Gaddum, 1931; Rosenblueth and Loco, 1937; Ravin, 1940; Alonso-de-Florida et al., 1963): this increased sensitivity has been shown to apply to skeletal and smooth muscle, ganglia and glands and is known as denervation supersensitivity.

In striated muscle, denervation supersensitivity is particularly marked, and the degree of increased sensitivity to the close arterial injection of acetylcholine has been estimated to be between 10- and 100,000-fold (Brown, 1937; Brown and Harvey, 1938; Kuffler, 1943; Nicholls, 1956) in the frog and the fowl, and 100–100,000-fold (Brown, 1937; Rosenblueth and Loco, 1937) in mammalian muscles.

Nicholls (1956) proposed that the increased sensitivity of striated muscle to acetylcholine and other chemicals is far greater than its increased sensitivity to electrical stimulation, and cannot be explained by changes in the electrical properties of the muscle membrane. Thus it would appear that supersensitivity following denervation results from an increase in the chemical excitability of the muscle with an enhanced responsiveness of a part of the muscle to the depolarizing action of acetylcholine.

There are three possible explanations for this suggestion:

(1) Prolonged and intensified action of acetylcholine on motor endplate receptors.
(2) An increase in the number and/or affinity of acetylcholine receptors in the motor endplate.
(3) An increase in the size of the acetylcholine receptor surface, beyond the normal motor endplate limits.

Several investigators (Cannon and Rosenblueth, 1949; Stromblad, 1956) have suggested that supersensitivity is caused by an intensified action of acetylcholine secondary to a decrease in cholinesterase activity in denervated muscle. Following denervation, however, a muscle is sensitized not only to acetylcholine but also to a similar degree to a number of other agents, which are not destroyed by these enzymes. Furthermore, no correlation is observed between the total amount of cholinesterase and the degree of supersensitivity (Brooks and Chipman, 1952; Brooks and Myers, 1952). Therefore, the enzyme theory can do little more than contribute to acetylcholine sensitization. In itself it cannot explain the phenomenon (Thesleff, 1960a).

In innervated adult skeletal muscle, Kuffler (1943) claimed that acetylcholine sensitivity existed only in the region of the neuromuscular junction. Miledi (1960a), however, showed that the chemosensitive properties of the muscle membrane in the frog extend beyond the neuromuscular junction, but that sensitivity falls off steeply, becoming several thousand times smaller within a few hundred microns of the junction.

Initial investigations suggested that increased sensitivity following denervation was indeed restricted to the denervated motor endplate area (Brown, 1937; Rosenblueth and Loco, 1937), but evidence for an increase in sensitivity along the whole length of the muscle fibre was obtained by Ginetzinsky and Shamarina (1942), Miledi (1960a, b) and Axelsson and Thesleff (1959). The last-named workers showed, in mammalian striated muscle, that 3–6 days after denervation the acetylcholine sensitive area covers the larger part, or all of the muscle membrane, which attains approximately the same sensitivity to acetylcholine as the endplate region prior to denervation. Acetylcholine then produces depolarization when applied to any part of the muscle membrane. They also showed that the original endplate region does not alter in sensitivity and is not affected by the process which renders the rest of the fibre sensitive to acetylcholine.

It may be postulated that as a result of denervation additional “receptors” are induced, or uncovered, in the muscle fibre. Whether the receptors “uncovered” in the muscle fibre are identical in their properties to those normally present at the endplate region is doubtful (Beránek and Vyskocil, 1967). Axelsson and Thesleff (1959) showed that while the new receptors respond in a manner qualitatively similar to that of the innervated endplate, they differ in their response to anticholinesterases. The authors inferred from this that the new receptors are practically devoid of cholinesterase.

The mechanism by which the receptor area increases is not known. Thesleff (1960b) believed that it is related to suppression of the normal action of acetylcholine on the muscle endplate; Miledi (1960a) suggested that it is due to some other neural influence on muscle, which may or may not be associated with acetylcholine transmission across the junction. Although recent experimental evidence (Katz and Miledi, 1961) has been presented to suggest that muscle injury itself is a cause of supersensitivity to acetylcholine, and that muscle can respond in this way regardless of whether it is innervated or not, it would appear that intact nerve endings exert a controlling influence along the whole length of the muscle fibre (Eccles, 1962) and are at least partially responsible for the development of endplates.
The actual muscular response to acetylcholine in chronically denervated muscle is probably dose-dependent (Brown, 1937; Peterson, Sternberg and Orndahl, 1962), but is usually a contracture (Brown, 1937; Peterson, Sternberg and Orndahl, 1962; Rosenblueth and Loco, 1937) rather than a contraction. There is much confusion between these terms and some authors have used them interchangeably. Contracture in a physiological and pharmacological sense has been defined by Gasser (1930); it denotes a reversible but sustained state of shortening or tension development, which lacks some of the features of muscular contraction. The main difference is that contracture may affect only part of the muscle fibre, and is not accompanied by a propagated action potential. A contracture-like response results from depolarization and is accompanied by the production of heat and lactic acid.

Although contracture has been defined in physiological terms, there is some doubt as to whether it is a physiological event, its mechanism of production is also open to debate. It has been cited as an example of the interdependence of the contractile and electrical phenomena in contraction, in that it represents the depolarization of an area of membrane sufficient to activate a contractile mechanism yet not sufficient to propagate an all-or-none disturbance. It would be an instance of contraction without conduction. This concept must be reconciled with the importance of sustained depolarization in the mechanism of contracture (Davson, 1970). The work of Axellson and Thesleff (1959) and Kuffler (1943) demonstrates that in denervated muscle the conversion of the muscle membrane into acetylcholine-sensitive surface would allow acetylcholine to depolarize the entire length of the muscle for a sustained period, owing to the absence of cholinesterase in this area.

Contracture is a part of the normal response to acetylcholine in certain frog and bird muscles in the healthy and denervated state (Brown, 1937; Brown and Harvey, 1938; Rosenblueth and Loco, 1957) in denervated mammalian muscle (Brown, 1937) and in botulinum-intoxicated cat muscle (Thesleff, 1960b). The muscle fibres in all these cases show an increase in the acetylcholine-sensitive surface (Axelsson and Thesleff, 1959; Miledi, 1959; Miledi, 1960b; Thesleff, 1960b). Thus, whatever the actual mechanism may be, a prerequisite for contracture is an increased acetylcholine receptor area (Orndahl, 1962b).

Foetal and newborn mammalian striated muscle fibres are of special interest, for it has been shown that they too differ in sensitivity to acetylcholine from adult muscles. Thus in a 19-day-old rat foetus, Diamond and Miledi (1959, 1962) demonstrated that striated muscle fibres are quite sensitive to acetylcholine over their entire surface, and that this increased sensitivity can be seen in some fibres 1–2 days after birth. The authors conclude that embryonic muscle fibres have a generalized sensitivity to acetylcholine before they receive their motor nerves, and the effect of innervation is to produce a reduction of sensitivity outside the neuromuscular junction; the receptor area to acetylcholine shrinks as maturation proceeds. Histological evidence is provided by Couteaux (1941) who found in kittens at birth that the nerve terminates at the surface of the muscle, and that the endplate region is not differentiated. Similarly, Orkand (1964) found that in kittens even a few weeks after birth only a few synaptic clefts can be demonstrated. It is possible that the receptor sites present before maturation are the same as the receptor sites “uncovered” by denervation (Diamond and Miledi, 1962).

In man contracture, as a response to depolarizing muscle relaxants, is seen in certain other conditions apart from chronic denervation. It has been demonstrated in dystrophia myotonica (Orndahl, 1962a; Orndahl and Sternberg, 1962) and myotonia congenita (Orndahl, 1962a; Orndahl and Sternberg, 1962). There are several reports in the literature of patients with dystrophia myotonica developing muscle rigidity (Kaufman, 1960; Orndahl, 1962b; Paterson 1962; Thiel, 1967), which may be generalized, following suxamethonium. In this condition the endplates tend to cover a larger surface area than normal (Coers and Woolf, 1959; Woolf, 1962), and it would seem reasonable to suggest that there is an increased receptor surface to acetylcholine. However, the pathology of this disease is complex and has been shown to involve nerve as well as muscle (MacDermot, 1961). Theoretically, in dystrophia myotonica non-depolarizing muscle relaxants, while not necessarily overcoming the rigidity, should not in themselves produce an abnormal effect. This would appear to be substantiated by the work of Orndahl (1962b) but there is no general agreement about the value or advisability of using non-depolarizing relaxants in this condition.

Contracture following suxamethonium has been reported also in a patient with amyotrophic lateral sclerosis (Orndahl, 1962b). This is interesting in view of Cannon's suggestion that hypersensitivity to chemical agents may be seen “if penultimate and
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possibly anti-penultimate neurones are destroyed". Perhaps what is surprising is the scarcity of reported cases in patients with disease or injury of the central nervous system. There is no evidence to link the contracture of denervation with the abnormal muscle rigidity, which may occur in the syndrome of malignant hyperpyrexia. In the latter condition recent evidence suggests that a defect in sarcoplasmic reticular calcium release and binding (Harrison, 1971; Kalow et al., 1970) is the factor which may be responsible.

Contracture can also occur in innervated muscle in man. Thus it is seen normally in the extra-ocular muscles, following injection of acetylcholine (Duke Elder and Duke Elder, 1930) and suxamethonium (Breinin, 1962). It is believed to be caused by stimulation of the slow muscle fibres (Eakins and Katz, 1965; Hess and Pilar, 1963). Histology of these fibres shows that they are innervated by multiple grape-like endings (Hess and Pilar, 1963), and thus presumably there is once again an enlarged acetylcholine receptor surface.

It is well recognized that supersensitivity can follow pharmacological denervation as well as surgical denervation (Emmelin, 1961). This has been advanced as an explanation for some drug interactions. More recently Collier (1969) has postulated that within the central nervous system a mechanism analogous to denervation sensitivity may be involved in the development of dependence and tolerance to narcotic analgesics.

It is suggested phylogenetically that contracture is the primitive forerunner of normal neuromuscular transmission found in mammalian muscle (Wylie and Churchill Davidson, 1972), and that supersensitivity of denervated organs has important consequences in that, although these organs do not receive nerve impulses, they react under certain conditions, and participate in generalized reactions of the organism (Cannon and Rosenblueth, 1949).

It is further possible that what we call supersensitivity in fact represents the genuine sensitivity of the cells, which, however, as long as these are connected with their nerves, is kept down by this influence. A nerve may thus have two functions; namely to conduct impulses, and to control the organ sensitivity (Locwi, 1946).

It is recommended that if muscle relaxants are to be used to produce relaxation in a part of the body which has suffered peripheral nerve damage, sufficient to cause nerve degeneration, then depolarizing relaxants should be avoided. Non-depolarizing relaxants should theoretically, in this situation, block transmission at the neuromuscular junctions which are still functioning normally, yet have no stimulating effect on the newly induced acetylcholine receptors.

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