# The Site of Action of Some Chemical Agents in Diminishing Normal and Excessive Muscle Tension[1, 2]

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The ability to reduce or to efface normal muscle tension or to lessen or abolish states of increased tension in muscle by the administration of drugs not only promises new knowledge concerning neuromuscular mechanisms, but also offers the possibility of aid to those suffering from disorders in which excessive muscular tension is a prominent and disabling feature. Furthermore, the determination of the exact site of action of chemical compounds on central neurons may ultimately lead to the successful utilization of appropriate substances in a number of disorders and diseases of the nervous system. Among the chemical agents which are known to possess the property of reducing muscle tension, curare and its derivatives, especially D-tubocurarine, the erythroidine compounds, and myanesin have received the most consideration.

The relaxing effect of curare on muscle tension is generally considered to be due to blockade of the motor nerve endings, and the degree of relaxation is thought to be in direct proportion to the number of motor nerve endings affected. Thus, the term curare-like action when applied to a drug is generally understood to mean that the drug is able to effect a partial or complete motor end-plate block. It is an important and well-known observation that partial blocking of the motor nerve endings in the extremity muscles can be attained with curare before paralysis of the respiratory mechanism. This affords a basis for the administration of curare in order to increase muscular relaxation during anesthesia for surgery.

The effect of curare on muscle function has been extensively studied by Bremer and his associates (*4–6*). They found that small doses temporarily abolished or considerably diminished the extensor rigidity of decerebrate cats, without significantly affecting phasic responses. This differential effect was explained on the hypothesis that light curarization activated the latent fatigue which existed at the neuromuscular junctions undergoing continuous bombardment by the tonic impulses, and hence altered the endings in such a manner that those impulses producing the rigidity were more easily blocked than those concerned with phasic responses. All available evidence supports the view that curare exerts its relaxing effect on muscle by action at the motor nerve endings. However, it should be possible to bring about reduction in muscle tension from action on central neural mechanisms. Our investigations on the two types of compounds, other than curare, which have been most used for reducing muscle tension—namely erythroidine and myanesin—have revealed the fact that in the case of these drugs a central action exists.

The erythroidine alkaloids were first isolated by Folkers and Major (*7*) and the initial pharmacological studies were made by Unna, Kniazuk, and Greslin (*11*), and Unna and Greslin (*12*). Of the Erythrina alkaloids isolated, both dihydro-β-erythroidine hydrochloride and β-erythroidine hydrochloride were found to possess a curare-like action, i.e., they abolished the contraction of striated muscle to excitation of its motor nerve fibers while the response to direct excitation of the muscle remained. In addition to confirming these findings of a curare-like action, we have found that the erythroidine compounds are able to exert a relaxing effect on muscle tension by central action. This effect is evident with doses considerably smaller than those producing complete end-plate blockade, but it becomes masked by larger doses which block transmission at the motor ending. In the normal nonanesthetized cat or monkey the administration of appropriate doses of either compound, orally or parenterally, produces muscular relaxation without abolishing spontaneous muscular movements or tendon reflexes. As the dose is increased, spontaneous movements disappear and greater relaxation of muscle tension is secured, but even with a considerable degree of muscular relaxation the tendon reflexes remain present, although reduced and easily fatigued, and the muscle contracts upon excitation of the muscle nerve. With still larger doses, the deep tendon reflexes are no longer elicitable, the animal becomes completely paralyzed, the muscle no longer responds to stimulation of its nerve, and paralysis of respiratory movements ensues. With the erythrodine alkaloids, the added amount of drug necessary to paralyze respiration after beginning muscular relaxation is large enough to afford a considerably greater margin of safety than in the case of D-tubocurarine and, as regards the two erythroidine compounds, the margin of safety is greater with β-erythroidine hydrochloride than with dihydro-β-erythroidine hydrobromide.

The amount of erythroidine required to produce different degrees of erythroidinization varies considerably and significantly as regards cat and monkey. In the nonanesthetized cat the amount of dihydro-β-erythroidine required to produce initial relaxation of muscle tension when given intravenously at the rate of 0.5 mg/min was found to vary considerably from animal to animal, ranging from 0.20 to 0.24 mg/kg. With continued administration, the degree of relaxation gradually increases until complete relaxation and abolition of spontaneous movements is attained with a dose of 0.4–0.5 mg/kg. Paralysis of respiratory movements ensues when 0.9–1.2 mg/kg has been injected. In contrast to these findings on cats, intravenous administration of the compound to monkeys (*Macaca mulatta*) at the rate of 1 mg/min was found to produce initial relaxation of muscle tension with 4–6 mg/kg. Practically complete relaxation with loss of spontaneous movements occurs when 7–8 mg/kg has been given, and respiratory movements cease after 8.2–11.4 mg/kg. It appears, therefore, that the amount necessary to produce a given effect varies considerably,

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[2] The erythroidine compounds were supplied by Merck and Co. and the myanesin by E. R. Squibb and Sons.

not only from genus to genus, but also among individuals of any one species.

For the initial studies of the effect of these drugs on increased muscle tension, the standard preparation of the decerebrate cat was utilized. In such an animal it has previously been shown by Smith (*10*) that the administration of either of the two erythroidine compounds causes a gradual and complete relaxation of the rigid extremities without abolition of the tendon reflexes and without paralysis of respiratory movements. The amount required to produce relaxation of muscle tension was found to be approximately the same as in the case of nonanesthetized animals. When the excessive tension is completely abolished, the tendon reflexes are still present and respiratory movements persist. Continued administration of the drug produces paralysis of respiratory movements with a dosage similar to that required in experiments on nonanesthetized animals. With the advent of respiratory paralysis, tendon reflexes are no longer elicitable even though adequate oxygenation is insured by artificial respiration. Retention of the tendon reflexes in the state of abolition of the abnormal muscular tension, and the finding that at this stage the muscle is excited by stimulation of its nerve, suggests the possibility that the initial relaxing effect of the erythroidine compounds is not due to motor end-plate block, but to action of the drug on the central nervous system. Further investigations support this view by revealing that the crossed extensor reflex is abolished before loss of the knee jerk, although in every instance the knee jerk is diminished and exhibits the fatigability seen when the compounds are administered to nonanesthetized animals.

We next directed our attention to myanesin (*o*-toloxy-1,2-propanediol) in order to determine if it possessed a more discrete differential action on neuromuscular mechanisms than had been observed with erythroidine. This compound, when administered in appropriate amounts, has been shown by Berger and Bradley (*1, 2*) and Berger (*3*) to produce muscular relaxation and paralysis in animals anesthetized with chloralose without cessation of respiratory movements and without abolition of the knee jerk. They also found that contraction of the muscle through excitation of its nerve was not abolished except with doses larger than those necessary to produce paralysis of the extremities. Our investigations designed to yield information concerning the locus of action of the drug were first conducted on nonanesthetized cats. Administration of an aqueous solution of myanesin intravenously at the rate of 10 mg/min was found to produce a progressive generalized decrease in muscle tension, resulting in its complete abolition and in the disappearance of all spontaneous movements when approximately 125 mg/kg had been injected. At this stage, respiratory movements continued and the knee jerks were still present, but the flexor withdrawal reflex to noxious cutaneous stimuli was abolished.

In experiments employing decerebrate cats, it was found that myanesin, like erythroidine, produced a progressive relaxation of the muscle tension to the point of complete abolition. The amount required was considerably less than that necessary to abolish tension in the nonanesthetized animal. Even at the stage of complete relaxation, the muscle responded to stimulation of its nerve and knee jerks were elicitable, although both crossed extensor reflex and flexor reflex were abolished.

Analysis of the above experiments naturally led to the conclusion that myanesin had a differential action on central mechanisms, leaving intact the myotatic reflexes as exemplified by the knee jerk, but rendering inactive the reflex path for the flexor and crossed extensor reflexes. Further delimitation of the field of activity was attained by use of spinal animals. In spinal cats, with level of transection through the lower thoracic region, appropriate amounts of myanesin were observed to exert the same discrete differential effect on the spinal reflexes as in the decerebrate animal.

The interpretation of these results in the light of present day concepts of spinal cord structure and function affords information even more definitive concerning the probable locus of action. Current concepts of functional organization of the spinal cord, largely influenced by the investigation of Lloyd (*8, 9*), hold to the view that the crossed extensor reflex, the flexor withdrawal reflex, and other somatic reflexes elicited in response to cutaneous stimuli are mediated over pathways containing internuncial neurons interposed between the entering afferent fibers and the motor neurons innervating the reacting muscles. On the other hand, myotatic reflexes, of which the knee jerks and ankle jerks are well known examples, are considered to be effected by the incoming afferent impulses exciting the somatic motor neurons directly without the intervention of interneurons. Inasmuch as our experiments clearly demonstrate that these several responses which at present are considered to involve internuncial activity are abolished by erythroidine and myanesin in appropriate amount, while the myotatic reflexes remain in effect, it seems likely that both drugs are able to exert a relaxing effect on muscular tension by action on spinal internuncial neurons in such a manner as to produce a partial or complete internuncial blockade. The precise manner by which this is brought about must be determined by further investigations.[3]

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[3] We have recently found that the administration of myanesin to the anesthetized cat abolishes movements of the extremities elicited by electrical stimulation of the motor cortex.