Pharmacological studies of extraocular muscles

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The effects of neuromuscular blocking agents and anticholinesterases on the twitch and tonic neuromuscular systems of the superior rectus muscle and the twitch system of the tibialis anterior muscle were studied in pentobarbital-anesthetized cats. The twitch system is characterized by large-diameter nerve fibers, plaque-like nerve endings, and Fibrillenstruktur muscle fibers; the tonic system by small-diameter nerve fibers, grape-like nerve endings, and Felderstruktur muscle fibers. Depolarizing agents (succinylcholine, decamethonium, Imbretil) increased baseline tension of the superior rectus muscle by their effect on the tonic system. Nondepolarizing agents (d-tubocurarine, dimethyl tubocurarine, gallamine) and depolarizing agents decreased the twitch response of the superior rectus and tibialis anterior muscles by their effect on the twitch system. Anticholinesterases increased the baseline tension and twitch height of the superior rectus muscle, but had a variable effect on the twitch height of the tibialis muscle. It is suggested that saccadic eye movements are a function of the twitch system, while slow sustained activity of the eye is accomplished by the tonic system.

This paper reviews some of our observations on the effect of drugs on the extraocular muscles. These studies were undertaken because of our interest in intraocular pressure. It became apparent in preliminary studies that the extraocular muscles played a significant role in controlling intraocular pressure. We therefore decided to study the extraocular muscles before undertaking studies of intraocular pressure. In reviewing what was known about extraocular muscles, we came across two apparently conflicting ideas. One was that the extraocular muscles of the cat and man were especially sensitive to neuromuscular blocking agents. Others, however, believed that the neuromuscular blocking agent, succinylcholine, was not capable of blocking the neuromuscular junction of the extraocular muscles.

Methods

Studies were carried out in cats anesthetized with sodium pentobarbital (36 mg. per kilogram) given by intraperitoneal injection. The trachea, femoral artery, and femoral vein were cannulated. The superior rectus muscle of the left eye was separated from the globe and a suture placed through the tendon. After the animal's head was immobilized in a stereotaxic apparatus, the tendon was attached to a Grass force displacement transducer (Model FT-03). Through a parietal craniotomy, the dura mater was opened, the left

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cerebral hemisphere lifted gently to expose the third nerve, and the nerve impaled with a needle electrode. Supramaximal stimuli consisting of rectangular pulses of 1 msec duration were delivered to the nerve from a Grass stimulator (Model SC4) at a frequency of 0.1 to 0.3 c.p.s.

The left sciatic nerve was isolated and ligated at mid-thigh level, and a shielded Palmer bipolar electrode applied to the peripheral end. Supramaximal stimuli consisting of rectangular pulses of 1 msec duration were delivered to the nerve from a Grass stimulator at a frequency of 0.1 to 0.3 c.p.s. The resulting twitch response of the anterior tibialis muscle was measured with a Grass force displacement transducer (FT-03).

Femoral arterial blood pressure was measured with a Statham pressure transducer. Recordings were made on a Grass polygraph. All animals were artificially ventilated with a Frumin-Lee respirator. Drugs were injected into the femoral vein.

Results and discussion

In Fig. 1, the effect of increasing doses of succinylcholine on the superior rectus muscle is seen. It can be observed that the initial effect is an increase in the baseline tension, with little or no effect on the twitch response. As the dose of succinylcholine is increased, there is a greater rise in baseline tension. However, the twitch response is now depressed and finally, at a dose of 128 μg per kilogram, abolished. Thus succinylcholine has a stimulant effect on the resting tension but a depressant effect on the twitch response. These results can be explained in terms of the two neuromuscular systems known to be present in certain muscles.

Sommerkamp in 1928 described two different responses of frog muscle to acetylcholine. One response was a rapid transient contraction (twitch) which he observed in the sartorius muscle. The other response was a slow maintained contraction, which was seen in the rectus abdominus muscle. Sommerkamp was able to separate the fibers of the ileofibularis muscle into a tonus bundle, which responded to acetylcholine with a slow maintained contraction, and into nontonic fibers in which acetylcholine produced a twitch response. Subsequently two different anatomical types of skeletal muscle fibers were described in the frog. One type (Felderstruktur) had large, poorly defined fibrils, while the other type (Fibrillenstruktur) had small, regular, well-defined fibrils. The
Felderstruktur characteristic of the tonus bundle had numerous, small, grape-like nerve endings, derived from small-diameter efferent nerves. The Fibrillenstruktur characteristic of twitch fibers had single, large, plaque-like nerve endings derived from large-diameter efferent fibers.

These two different morphological systems differed in their electrophysiological and mechanical properties. Stimulation of the small-diameter (5 μ) ventral root nerve fibers resulted in slow graded muscle contractions which were accompanied by nonpropagated muscle potentials of small amplitude and long duration. These small nerve fibers could not be excited by single stimuli, but required tetanic rates of stimulation. Stimulation of the large diameter (12 μ) ventral root nerve fibers produced motor unit twitches accompanied by fast, propagated muscle action potentials. The two neuromuscular systems are now known to be present in the extraocular muscles of the cat, monkey, and man.

We believe that the responses to succinylcholine, as well as other depolarizing agents (decamethonium and Imbretil—see below) can be explained in terms of the two neuromuscular systems discussed above. The increase in baseline tension is attributable to the tonic system and the decrease in twitch response to the twitch system.

The dose of succinylcholine required to

![Graph showing the effect of increasing doses of succinylcholine on the superior rectus muscle (S.R.) tension and twitch response and the tibialis anterior muscle (T.A.) twitch response. Note depression of tibialis muscle twitch after 8 μg per kilogram and depression of superior rectus muscle twitch after 64 μg per kilogram. All doses in micrograms per kilogram.](https://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/933621/)
decrease the twitch response of the extra-ocular muscles appeared to be much greater than that usually required to depress the twitch response of the tibialis muscle. In order to confirm this, the effect of succinylcholine on the twitch responses of the tibialis anterior and superior rectus muscles were simultaneously determined in the same animal. A representative result is shown in Fig. 2. The effect on the superior rectus muscle is similar to that seen in Fig. 1. It can also be seen that the twitch response of the tibialis anterior muscle was depressed by a smaller dose of succinylcholine than that required to depress the twitch response of the extraocular muscles. Thus the extraocular muscles, rather than being unusually sensitive to succinylcholine, are unusually resistant to this drug. Unlike Linkoff and co-workers, we were able to show a neuromuscular blocking action of succinylcholine on the extraocular muscles. Their failure to do so is probably attributable to the fact that the maximum dose used in that study was 50 \( \mu \text{g} \) per kilogram. Although this dose markedly depressed the tibialis twitch response, it rarely was sufficient, in our study, to depress the twitch response of the extraocular muscles.

In Fig. 3, the effect of increasing doses of decamethonium can be seen. The results are similar to those described for succinylcholine in that the superior rectus baseline tension is increased, the twitch response of the tibialis anterior is depressed, and the twitch response of the superior rectus is depressed. However, the results with decamethonium differ from those seen with succinylcholine in that the...
dose of decamethonium required to depress the superior rectus twitch response was not greatly different from that required to depress the tibialis anterior twitch response. With succinylcholine, the dose required to depress the superior rectus twitch response was usually 8 to 16 times greater than that required to depress the tibialis anterior twitch response. In order to determine whether this was a true difference in sensitivity of the two muscles to the neuromuscular blocking action of succinylcholine as compared with decamethonium, the effects of these agents were determined in the same animal. In Fig. 4, the effect of succinylcholine is shown. This is the same animal depicted in Fig. 3. A comparison of the results makes it clear that the superior rectus and tibialis anterior muscles differ in their relative sensitivity to succinylcholine and decamethonium.

Imbretil (1 to 16 μg per kilogram produced results similar to those seen with succinylcholine and decamethonium. The difference in sensitivity of the superior rectus and tibialis anterior muscles to depression of the twitch response by Imbretil was less than seen with succinylcholine.

Next we will consider the effect of the nondepolarizing agents. These include d-tubocurarine, dimethyl tubocurarine, and gallamine. Fig. 5 demonstrates that repeated doses of d-tubocurarine decrease the twitch response of the superior rectus muscle. In addition, the baseline tension of this muscle was increased, a result seen in approximately 50 per cent of the animals studied. It had been reported that extraocular muscle behaves in a fashion similar to denervated muscle, which responds to d-tubocurarine with an increase in muscle tension.20-23

The decrease of the superior rectus mus-

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**Fig. 4.** Same cat as in Fig. 3. Effect of increasing doses of succinylcholine on the superior rectus muscle (S.R.) tension and twitch response and the tibialis anterior muscle (T.A.) twitch response. Note increase in superior rectus tension after 1 μg per kilogram, decrease in tibialis twitch after 16 μg per kilogram, and decrease in superior rectus twitch after 128 μg per kilogram.
d-TUBOCURARINE
25 μg/kg at each

Fig. 5. Effect of d-tubocurarine on the superior rectus muscle (S.R.) tension and twitch response. Note increase in baseline muscle tension.

Fig. 6. Effect of d-tubocurarine on the superior rectus muscle (S.R.) and tibialis anterior muscle (T.A.) twitch response. Note greater depression of tibialis anterior muscle twitch response.

cle twitch produced by d-tubocurarine (Fig. 5) did not seem to indicate an unusual sensitivity of the muscle to this drug. To clarify this point, the effects of d-tubocurarine on the tibialis anterior and superior rectus muscles were simultaneously determined in the same animal (Fig. 6). The superior rectus muscle was not unusually sensitive to d-tubocurarine, but rather showed less depression than the tibialis anterior muscle. This result is different from that reported by Brown and Harvey.5 They did not compare the dose of d-tubocurarine required to block the limb and eye muscles in the same animal, except in one case. In this animal, the response of the extraocular muscle to approximately 200 μg per kilogram of d-tubocurarine was similar to that seen in the present experiment. However, the tibialis anterior twitch response was unaffected. In our experience as well as that of others, the tibialis twitch response would usually be depressed by 200 μg per kilogram of d-tubocurarine.

The effects of dimethyl tubocurarine and gallamine on the tibialis anterior and superior rectus muscles are shown in Figs. 7 and 8. In none of the animals studied did either drug increase the baseline tension. Although there were variations in the magnitude and duration of action of these two drugs on the tibialis anterior muscle as compared with the superior rectus muscle, we do not feel that the differences are very large. The sensitivity of the two muscles to both drugs is approximately similar.

The effects of edrophonium and neostigmine were also studied. These agents increased the twitch response of the superior rectus muscle and usually increased the tension of the superior rectus muscle. Thus, edrophonium and neostigmine stimulated both the twitch and tonic neuromuscular systems of the extraocular muscles. Their effects on the tibialis anterior muscle...
Fig. 7. Effect of gallamine on the superior rectus muscle (S.R.) and tibialis anterior muscle (T.A.) twitch responses. Note difference in magnitude and duration of block in response of cat shown in A as compared with that of another cat shown in B. In each animal, the magnitude of block of tibialis and superior rectus muscle was similar but the duration of action was greater for the tibialis muscle.

Fig. 8. Effect of dimethyl tubocurarine on the superior rectus muscle (S.R.) and tibialis anterior muscle (T.A.) twitch responses. A: Note more rapid onset of block as well as recovery in the superior rectus muscle. B: Note that in this animal the onset and magnitude of block of both muscles were similar, with a more rapid recovery of tibialis muscle.
were variable. Either a decrease or an increase in tibialis anterior twitch height could be observed.

We should like to speculate briefly on the possible role of the two neuromuscular systems which are present in the extraocular muscles of man, as well as the cat. The eye is frequently required to make rapid saccadic movements, which may be observed.

Either a decrease or an increase in tibialis anterior twitch height could be observed.

The eye is frequently required to make rapid saccadic movements, which may be a function of the twitch system. The slow sustained activity of the eye may be accomplished by the tonic system. In addition to these two neuromuscular systems present in extraocular muscle, studies in our laboratory suggest that another system, possibly sympathetic, may be present in the extraocular muscles of the cat and man.

REFERENCES