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Drug Actions at Mammalian Motor Nerve Endings: The Suppression of Neostigmine-induced Fasciculations by Vecuronium and Isoflurane

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The occurrence of fasciculations following administration of anticholinesterase agents is a well-known pharmacologic phenomenon. Using the cat soleus nerve-muscle preparation, intravenous neostigmine doses between 20–200 μg/kg evoked fasciculations in a dose-related manner. The data demonstrate that the fasciculations were the result of the direct effect of neostigmine acting at the motor nerve endings. Vecuronium in a dose-related manner (3 and 5 μg/kg iv) suppressed this prejunctional activity of neostigmine. The prejunctional effect of vecuronium explains its effectiveness in preventing succinylcholine-induced fasciculations. In the presence of isoflurane (end-tidal concentration 0.20–0.25%), the suppressant effect of vecuronium on motor nerve endings was enhanced. The prejunctional action of isoflurane may be a major contribution to the additive effects of non-depolarizing muscle relaxants and potent inhalation agents. (Key words: Anesthetics, volatile: isoflurane. Antagonists, neuromuscular: neostigmine. Neuromuscular junction: motor nerve endings. Neuromuscular relaxants: prejunctional site of action; vecuronium. Muscle, skeletal: fasciculations.)

IN MAMMALIAN NERVE-MUSCLE preparations, administration of anti-cholinesterase agents, such as edrophonium and neostigmine, is regularly followed by fasciculations. These drug-induced fasciculatory contractions are thought to originate at motor nerve endings.[1–5] In this context, motor nerve endings are that portion of the peripheral motor axons extending from the distal or last node of Ranvier, and include the unmyelinated terminals. Although the phenomenon is fairly well known, no dose-response relationships in the cat between this class of drugs and fasciculations have been demonstrated.

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This study was undertaken to establish the dose-response relationship between neostigmine dose and fasciculations, and to determine the site of action for this effect. Since subthreshold blocking doses of non-depolarizing muscle relaxants are administered to prevent succinylcholine-induced fasciculations, the effects of vecuronium on neostigmine-induced fasciculations were studied. The additive effect of the potent inhalation anesthetic, isoflurane, on the vecuronium suppression of the neostigmine-induced fasciculations was studied since the potency of non-depolarizing neuromuscular blocking drugs is enhanced in the presence of a potent inhalation agent.

Materials and Methods

The surgical technique employed in this study has been well described previously.[4,6] Briefly, an *in vivo* soleus nerve-muscle preparation was made in cats anesthetized with alpha-chloralose, 90 mg/kg iv. The soleus muscle was partially freed from the underlying muscle, and a piece of soft, thin, flexible, inert plastic was inserted between the muscles to isolate the soleus muscle from electrical events occurring in other skeletal muscles. The soleus tendon was connected to a strain gauge to record the muscle contractile responses. The soleus nerve was briefly stimulated supramaximally at 0.4 Hz with a rectangular pulse of 0.1 msec duration to adjust the soleus muscle for isometric tension. Stimulation was then stopped, and the muscle was rested for 30 min before the administration of neostigmine.

A silver needle electrode was placed in the belly of the soleus muscle, and another silver electrode was inserted in the tendon. A dorsal laminectomy exposed ventral roots L6, L7, and S1, which were cut proximal to the spinal cord. The soleus alpha-motor axons contained in the ventral roots were identified, separated, and gathered to form one large bundle which was placed on a platinum recording electrode. The surgical wounds in the leg and back were covered with paraffin oil maintained at 37° C by radiant heat.

The connection of the soleus muscle to the force transducer, the silver needle electrodes in the soleus muscle, and the placement of the soleus ventral root on the platinum electrode made possible the recordings of, respectively, the soleus muscle contractile fascicula-

tions, the soleus muscle fascicular electromyograph (EMG), and the antidromic action potentials of the soleus motor nerve. The output of the transducer amplifier was connected in parallel to an integrator which made possible quantitation of the entire muscular contractile fasciculations in arbitrary units. Neural action potentials which originate at locations other than the axonal hillock of the motor nerve are propagated in opposite directions from their point of origin. The orthodromic action potentials result in neuromuscular transmission of motor units. The antidromic action potentials travel up the axon into the ventral root, from which they can be recorded by platinum recording electrodes. Both the action potentials detected in the ventral roots and the EMG action potentials were recorded on a tape recorder and later played into a signal averager which computed the number of events occurring in 1 s (peak average rate), and also counted the total number of events which occurred during the entire experiment.[4] Drug effect was considered to have ceased if no activity occurred for 3 min, at which time the recording was stopped.

In another series of experiments, single soleus axons which innervated motor units on the surface of the soleus muscle were isolated in the ventral root. One at a time, these were placed on the platinum recording electrode, and, at the same time, an insulated concentric recording electrode was placed in the muscle fibers innervated by that single ventral root axon to record the motor unit EMG. This allowed simultaneous recording of the muscle and nerve electrical activities from a single motor unit. Recordings were made from two different matched single motor units in each cat. No muscle contractile fasciculations were recorded in this series, since the technique used to record this activity in whole muscle was not selective for recording the fascicular activity of a single motor unit. The neostigmine dose used in this series was 20 μg/kg. This dose was selected to minimize recording difficulties encountered using larger doses: the movement of the muscle electrode and correlation of the large number of neural and muscle action potentials which occurred at peak activity.

Thirty-four cats of either sex were used in the entire study. Neostigmine and vecuronium were administered intravenously with each animal receiving only one dose of neostigmine or vecuronium and neostigmine, with one exception: the matched ventral root axon and motor unit experiments. Here, two doses of neostigmine (20 μg/kg) were administered to each of two cats, with the minimum waiting period between injections being 90 min. All animals received atropine sulfate 1 mg/kg. Vecuronium, when given, was injected intravenously 10 min before the administration of neostigmine. Isoflurane, when given, was administered for 5

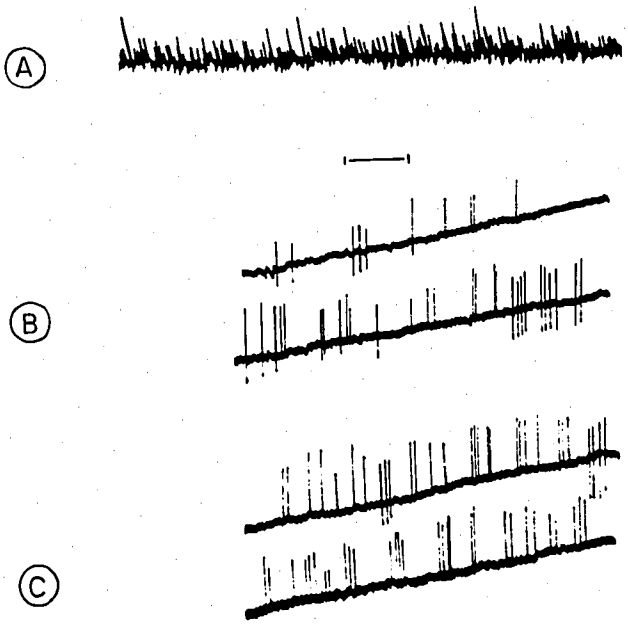

FIG. 1. Typical fasciculations and the accompanying asynchronous action potentials (AP) induced by neostigmine 50 μg/kg iv given 7 min earlier. *A*. Fasciculations. *B*. Muscle APs. *C*. Neural APs. The time scale for *A* is 10 s. Each sweep of *B* and *C* represents 200 msec.

min at an end-tidal concentration of 0.8%. It was then changed to 0.20% (range 0.20–0.25%), and administered for another 20 min before the injection of vecuronium. The concentrations of the neostigmine, vecuronium, and atropine sulfate solutions were such that the desired dose per kg was contained in 1 ml. Neostigmine was used as the fasciculation-inducing agent, due to its long duration of action, which provided ample opportunity for measuring and assessing drug effects.

Data were analyzed using Student's *t* and Chi-square tests, with $P < 0.05$ considered significant. Dose regressions were determined using the least-square method.

Results

Figure 1 shows typical fasciculations, EMG, and neural discharges induced by neostigmine. These tracings were recorded from a cat which had received a neostigmine dose of 50 μg/kg 7 min earlier. In this animal, the activity was near its peak. Initially following neostigmine injection, the first activity was observed in the nerve: spontaneous single action potentials. Following this, single and pairs of spontaneous nerve and muscle action potentials were recorded, and muscular fascicular activity began. At first, the fascicular activity in muscle was small, and then grew in intensity and height until, at peak, it was similar to that seen in tracing 1A. At peak activity, trains of three or more repetitive neural and muscle action potentials were regularly ob-

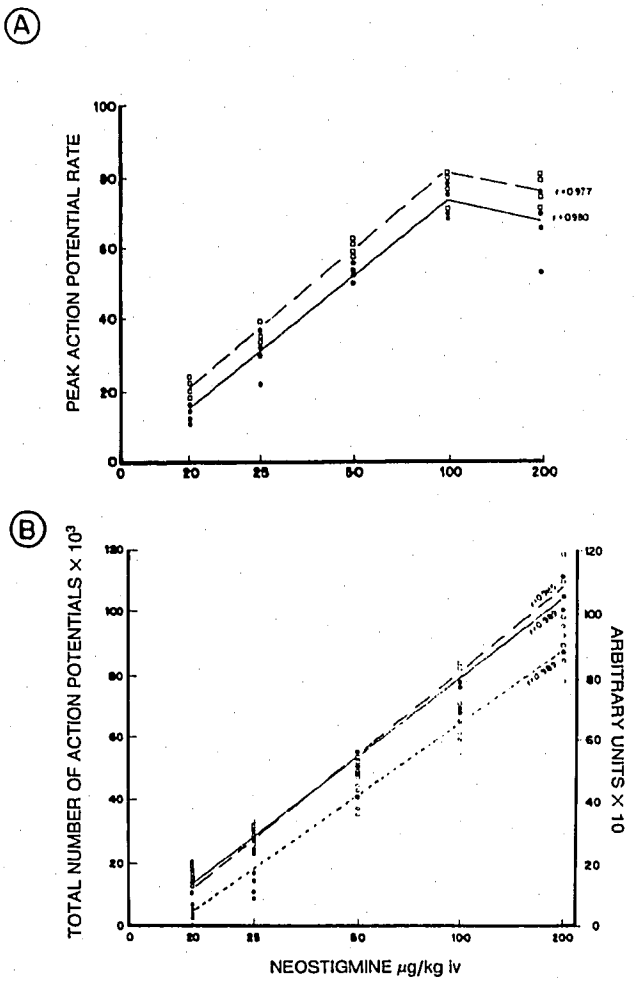

FIG. 2. Dose-response regressions. *A.* Peak rate (average no. of events per second) of muscle (y = 81.127 log X − 86.824, r = 0.980, $P < .001$) and neural action potentials (y = 86.627 log X − 90.634, r = 0.997, $P < .001$) induced by neostigmine 20–100 μg/kg. *B.* Total activity (total number of events) of contractile fasciculations, arbitrary units, (y = 86.059 log X − 108.124, r = 0.989, $P < .001$), muscle action potentials (y = 83.261 log X − 91.542, r = 0.989, $P < .001$), and neural action potentials (y = 86.843 log X − 94.834, r = 0.985, $P < .001$) induced by neostigmine 20–200 μg/kg. Open circles = fasciculations; solid circles = muscle action potentials; open squares = neural action potentials.

served. As the drug effect waned, the trains of three or more occurred less frequently. Then, only single and, occasionally, double action potentials were observed. Usually muscular fascicular activity ceased shortly before all neural activity stopped.

The intensity of the neural, EMG, and fascicular responses increased directly with larger neostigmine doses. This was demonstrated by counting the average activity at peak (fig. 2A) or by measuring the cumulative activity during the entire experiment (fig. 2B). The threshold dose was 20 μg/kg. Doses larger than 100 μg/kg did not produce any further increase in the peak rate of either EMG or neural activity. The cumulative activity showed, however, further increases at a dose of 200 μg/kg. The effects of neostigmine doses larger than 200 μg/kg were not studied, since these doses were in the lethal range.

Table 1 lists the time course of fasciculations, EMG, and neural activity evoked by the various doses of neostigmine. Depending upon dose, the time from injection to peak activity ranged from 3.1–8.2 min. As the dose was increased, the time to peak was shortened. Not surprisingly, as the dose was increased, the total duration of activity was increased. This accounts for the increase seen in the cumulative activity between the 100 and 200 μg doses when no further increase was seen in the average peak rate of the action potentials.

Figure 3 shows the relationships between 1) the total neural and muscle action potential activities, and 2) the total fascicular activity and total neural action potential activity. The correlations of these relationships are, respectively, 0.996 and 0.968, thereby strongly suggesting a cause-and-effect relationship between neural events and muscle fascicular activity.

To confirm that the neural activity was responsible for the muscle fasciculations, a total of four matched axons and motor unit pairs were examined in two cats. Figure 4 shows a typical recording. The neostigmine dose used in this series of experiments was 20 μg/kg iv, and only the EMG and neural activity were recorded (see Materials and Methods). The spontaneous action potentials occurred not only singularly, but also in doublets and in triplets. The incidence of neural action potentials evoking complete and full corresponding mus-

TABLE 1. Time Course* of Neostigmine-induced Contractile Fasciculations, Muscle Action Potentials (MAP), and Neural Action Potentials (NAP)

Neostigmine† Dose (μg/kg iv)		Time‡ to Peak (min)	Duration ‡ (min)
20	Fasciculations	8.2 ± 0.5	47.4 ± 0.4
	MAP	7.7 ± 0.5	48.2 ± 1.2
	NAP	7.7 ± 0.4	48.1 ± 1.3
25	Fasciculations	7.5 ± 0.5	49.0 ± 0.7
	MAP	7.1 ± 0.5	50.8 ± 1.2
	NAP	6.8 ± 0.4	51.1 ± 1.7
50	Fasciculations	4.4 ± 0.3	69.5 ± 2.9
	MAP	4.1 ± 0.3	72.1 ± 3.1
	NAP	3.8 ± 0.3	71.6 ± 2.9
100	Fasciculations	3.7 ± 0.2	91.7 ± 3.4
	MAP	3.4 ± 0.2	94.6 ± 2.7
	NAP	3.3 ± 0.2	93.6 ± 3.4
200	Fasciculations	3.8 ± 0.1	147.0 ± 6.1
	MAP	3.2 ± 0.1	149.5 ± 6.5
	NAP	3.1 ± 0.1	150.4 ± 4.0

* Mean ± SEM.
† n = 4 cats at each dose.
‡ Measured from the time of the neostigmine injection.

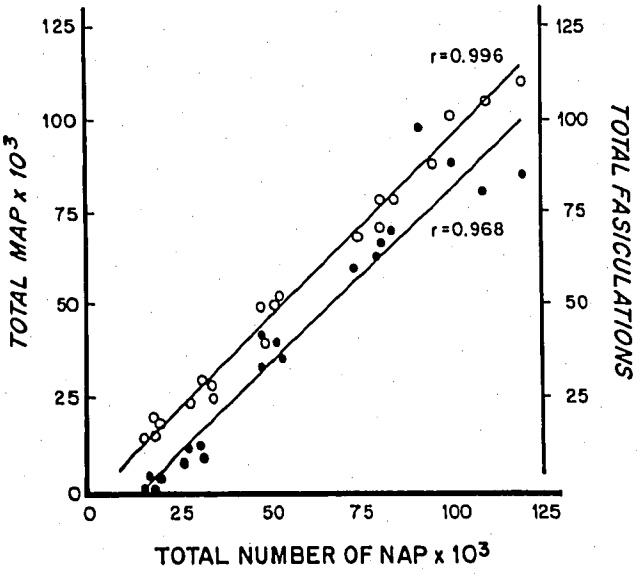

FIG. 3. Correlations between: 1) nerve action potentials (NAP) and muscle action potentials (MAP), open circles, $Y = 0.9565X - 0.716$, $r = 0.996$, $P < .001$; and 2) NAPs and contractile fasciculations, solid circles, $Y = 0.966X - 14.014$, $r = 0.968$, $P < .001$.

cle action potentials was 88.7% (table 2). On various occasions, the second or third neural action potential in a repetitive train did not evoke any, or only a partial, corresponding muscle action potential. The frequency of the train of nerve action potentials was such that the second or third neural action potential occurred during the absolute or relative refractory period of the muscle, and this resulted in none, or only a partial, muscle action potential. The incidence of this type of occurrence was 8.0%. On a few occasions, single neural action potentials occurred without evoking any muscle response (2.6%). This was probably due to either desensitization or transmitter failure.[7,8] A few single muscle action potentials (0.7%) occurred without any provoking event occurring in the nerve. This could be due to blockage of

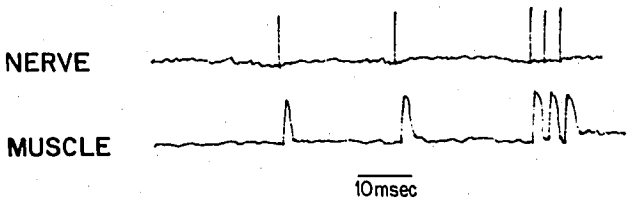

FIG. 4. Typical fascicular activity induced by neostigmine 20 μg/kg iv. Electrical activity recorded from a single soleus motor unit: upper tracing = neural actions potentials; lower tracing = muscle action potentials.

motor axon conduction proximal to its main branching, and would result in blocking the antidromic action potentials.[9]

Pretreatment with vecuronium suppressed the occurrence of the neural action potentials evoked by neostigmine. A 5-μg/kg dose of vecuronium administered 10 min before the administration of a 50-μg/kg dose of neostigmine completely prevented the occurrence of any neural action potentials, as well as any muscle action potentials and muscle fasciculations (table 3). A vecuronium dose of 3 μg/kg reduced (62.7%) the peak rate of neural action potentials from 60.25 to 22.5 events per second. The total duration of action was also decreased, and the total neural activity was reduced (64.1%) from 50.2 to 18.0×10^3 events.

In the presence of isoflurane, end-tidal concentration 0.20–0.25%, the 3-μg/kg pretreatment dose of vecuronium completely suppressed all neural activity (table 3). No muscle fascicular activity was observed.

Discussion

Fasciculations induced by neostigmine are the result of the initial random depolarization of unmyelinated nerve terminals.[5] With depolarizations of sufficient magnitude and duration, action potentials are generated at the distal node of Ranvier as a consequence of current flow from this region to the depolarized nerve

TABLE 2. Incidence of Single and Repetitive Neural (NAP) and Muscle (MAP) Action Potentials* Induced by Neostigmine, 20 μg/kg iv

	No. of Occurrences	% of Occurrences	No. of NAP	No. of MAP
Matched single NAP & MAP	364	66.5	364	364
Matched double NAP & MAP	108	19.7	216	216
Matched triple NAP & MAP	13	2.4	39	39
Total matched pairs	485	88.7	619	619
Double NAP & only 1 MAP	23	4.2	46	23
Triple NAP & only 2 MAP	21	3.8	63	42
Total NAP & some repetitive MAP	44	8.0	109	65
Single NAP & no MAP	14	2.6	14	0
Single MAP & no NAP	4	0.7	0	4
Total	547	100	742	688

* Data from two matched motor unit experiments, two matched pairs per cat.

TABLE 3. Effects of Vecuronium and Isoflurane on Spontaneous Neural Action Potentials Evoked by Neostigmine (50 μg/kg iv)

Pretreatment*	Peak Rate (event/s)	Total Activity ($\times 10^3$)	Time to Peak (min)	Total Duration† (min)
Neostigmine Control	60.25 ± 1.1	50.20 ± 1.1	3.8 ± 0.2	71.6 ± 2.9
Vecuronium (5 μg/kg iv)	-0-‡	-0-‡	—	—
Vecuronium (3 μg/kg iv)	22.5 ± 3.3‡	18.0 ± 4.8‡	3.9 ± 0.2	34.3 ± 8.0‡
Vecuronium (3 μg/kg iv) and Isoflurane (0.20–0.25%)	-0-§	-0-§	—	—

* n = 4 cats for each pretreatment and control.
† Measured from the time of the neostigmine injection.
‡ Pretreatment *vs.* control, $P < 0.05$.
§ Vecuronium and Isoflurane *vs.* Vecuronium 3 μg/kg, $P < 0.05$.

terminals. Repetitive firing ensues if the current flow is maintained for a sufficient time and the threshold of the distal node is reached. Thus, the neural activity evoked by neostigmine is a result of two actions on nerve endings. The first is the initial depolarization. If the current flow between the last node of Ranvier and the depolarized nerve terminal is of sufficient strength and duration, repetitive neural firing occurs. Transmission of these neural events to the muscle results in fasciculations. Since the occurrence of these neostigmine actions within a population of nerve endings is random, the results are asynchronous contractions of the individual motor units of the entire skeletal muscle. If the resulting muscle activity were due to the accumulation of acetylcholine at the endplates of individual muscle fibers, the resulting muscle activity would much more likely be fibrillations and not fasciculations.

The increase in intensity of the neural activity with neostigmine is reflected in the increase in the EMG activity and, as a consequence, as an increase in the fasciculations occurring within the muscle. Since fasciculations are coordinated events (non-coordinated events would result in fibrillation), their occurrence indicate that a pacemaker is driving the muscle fibers of a fascicle in unison. The most appropriate pacemaker is the motor nerve innervating the fascicle.[10] In fact, the fasciculations which are evoked by physostigmine in innervated skeletal muscle do not occur in denervated muscle.[11] Neostigmine has a permanently charged quaternary nitrogen, and readily reacts with the unmyelimated motor nerve terminals. An alternative to the direct effects of neostigmine on motor nerve endings is that these effects are due to the direct action of acetylcholine on nerve endings. Yet Riker has demonstrated that the doses which evoke fascicular activity regularly block neuromuscular transmission, and that exogenous acetylcholine can not duplicate the intensity or time course of the activity evoked by neostigmine.[12]

The ability of vecuronium to suppress the neural events which evoke a fascicular response in the muscle demonstrates a prejunctional effect of vecuronium. Other prejunctional effects of vecuronium have been established: the enhancement of tetanic fade, the suppression of neural post-tetanic repetition, and the capacity to evoke post-drug repetition.[13,14] Other non-depolarizing relaxants have similar effects on tetanic maintenance in humans, and suppress the neural repetitive generating capacity of cat soleus motor nerve endings.[15,16]

The fasciculations caused by depolarizing agents like succinylcholine, and by anticholinesterase agents like neostigmine, are due to the prejunctional actions of these drugs.[3,9] Clinically, subthreshold blocking doses of non-depolarizing muscle relaxants are administered to prevent the fasciculations caused by succinylcholine. The ability of non-depolarizing agents to prevent their occurrence is due to a prejunctional site of action of this class of drugs.

Vecuronium has been shown to interfere with transmitter release and, in regard to this action, is similar to other non-depolarizing muscle relaxants.[17,18] This prejunctional effect of non-depolarizing relaxants can explain the increased tetanic fade which occurs with these agents.[19] The ability to suppress fasciculations, however, appears to be related to the stabilizing effect of vecuronium and other non-depolarizing muscle relaxants on the motor nerve ending membrane, thereby preventing the initial depolarization of the ending by cholinergic agents.[20]

In the presence of isoflurane, the suppressive effect of vecuronium on the neostigmine-evoked neural activity is enhanced. Isoflurane also has been shown to enhance tetanic fade in humans, and to suppress post-tetanic repetitive activity in cats, both prejunctional actions.[21] The fact that isoflurane enhances the prejunctional effects of vecuronium strongly suggests a prejunctional action of this inhalation agent.

The experimental technique[22] of recording antidromic action potentials from the ventral roots gave early demonstrations of the prejunctional effects of various drugs which enhanced and attenuated synaptic function.[10,23,24] Although this technique does not measure synaptic transmission parameters, it is the only technique which provides direct monitoring of neural events *in vivo*. A modification of this type of neural recording is the matched pair technique, in which

recordings are made from both a single axon and the motor unit innervated by that axon. The results of the matched pair experiments clearly establish that the neostigmine-induced fasciculations arise prejunctionally.

Using an *in vitro* animal model, Waud and Waud[25] demonstrated that potent inhalation anesthetics depress the depolarization of the end plate by carbachol. Using the same animal model, these investigators[26] also reported that isoflurane (3.5–5.0 MAC) depresses the indirectly stimulated guinea pig lumbrical muscle responses, and that this depression occurred when the anesthetic concentration was sufficient to attenuate depolarization by 50%. The drug effects reported by Waud and Waud are post-junctional. This is evidence that potent inhalation anesthetics, like isoflurane, affect all excitable tissues. The results of the present study establish that isoflurane depresses fasciculations at lower concentrations than those which depress the depolarization of the end plate, and demonstrate a dose selectivity for the prejunctional or neural site of action. Thus, at those concentrations which depress the depolarization of the end plate, the motor nerve endings are always affected.

In summary, the following was found. First, as the dose of neostigmine is increased, the peak rate and the total number of fasciculations are increased. The data establish a dose-response relationship between neostigmine and fasciculations in the cat soleus muscle. Second, the data from the matched pair experiments demonstrate that the primary site of the fascicular action of neostigmine is at the motor nerve ending. Third, vecuronium in a dose-related manner suppresses the neural action potentials evoked by neostigmine at motor nerve endings. This reflects a prejunctional effect of vecuronium. And, fourth, in the presence of isoflurane, prejunctional potency of vecuronium is increased.

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