NEUROMUSCULAR PHARMACOLOGY:[1,2,3] DRUGS AND MUSCLE SPINDLES

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This review is limited to a consideration of the direct and indirect actions of drugs on muscle spindle function. A detailed description of the various sensory endings, their characteristic responses to stimuli, and the function of these receptors in reflexes is outside the scope of this review. These topics have been discussed in a recent symposium (8) and other reviews (34, 47, 64, 76, 95).

The mammalian muscle spindles are of particular interest since they contain the afferent ending for one of the basic reflexes, the stretch reflex. In addition to a complicated afferent system of one or more stretch sensitive endings, they possess specialized *intrafusal* muscle fibers which function as regulators of the sensitivity of the afferent receptor endings. The assessment of drug effects upon these intrafusal fibers has, by necessity, been limited to indirect methods. Stimulation of the small, high threshold myelinated fusimotor[4] nerves innervating the intrafusal muscle fibers results in an increase in the frequency of discharge of spindle afferent nerves as well as an increase in the sensitivity to stretch of the sensory ending with, however, no alteration in gross muscle tension.

It has not been proven that intrafusal neuromuscular (n-m) transmission is cholinergic but all data obtained to date are consistent with this assumption. The endplates contain cholinesterase (30, 31, 32, 75, 89), transmission is blocked by extrafusal anticholinergic blocking agents (table I), and anticholinesterases facilitate transmission (90) and antagonize tubocurarine block (54, 55, 80).

Agents acting directly on spindles.—Tubocurarine, its dimethylether, and gallamine have been reported to block intrafusal n–m transmission (Table 1). The intrafusal fibers appear to be less sensitive than the extrafusal; however, the difference in sensitivity is not great and it is difficult to block all extrafusal fibers and leave intrafusal n–m transmission unaffected (54, 55). Succinylcholine (SCh) rather selectively blocks extrafusal n–m trans-

[1] The survey of the literature pertaining to this review was concluded May 1962.

[2] Abbreviations used in this chapter include: ACh (acetylcholine); n-m (nerve-muscle, neuro-muscular); SCh (succinylcholine).

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[4] The term, fusimotor, will be generally used to denote the motor neuron or nerve fibers innervating the intrafusal muscle cells as suggested by Hunt & Paintal (94) in place of *gamma* or small motor nerve designations used previously.

TABLE I

OUTLINE OF DRUG ACTIONS ON MUSCLE SPINDLES

Drug	*Action Reported*	*Preparation and References*
Tubocurarine	N-m block of intrafusal fibers generally less than that of extrafusal	Frog or toad (103, 53, 54, 80, 138, 141) Cat (69)
	No detectable difference in sensitivity of intra- and extrafusal fibers to block	Cat-M. tenuissimus (55)
	Antagonizes sensory ending excitation produced by acetylcholine or succinylcholine	Frog (141) Cat (69, 90, 140)
	Does not abolish spindle stimulating effect of acetylcholine and succinylcholine	Frog (80)
	Reversibly abolishes spontaneous contractions and intrafusal muscle potentials	Frog (27)
Gallamine	N-m blockade; intrafusal fibers less sensitive than extrafusal	Frog (80) Rabbit (71)
	No consistent detectable difference in sensitivity of extra- and intrafusal fibers to block	Cat-M. tenuissimus (55)
Succinylcholine	Increase in discharge frequency of fibers from primary and secondary endings	Frog (81) Cat (69, 59, 58, 21, 82, 83, 84, 86, 78)
	N-m block of extrafusal fibers more marked than that of intrafusal	Rabbit (38)
Acetylcholine	Decrease in afferent nerve discharge frequency (intrafusal muscle fibers destroyed)	Frog (121)
	Increase in afferent discharge frequency	Cat (90)

TABLE I (*Continued*)

Drug	*Action Reported*	*Preparation and References*
Decamethonium	Increase in tonic discharge frequency of fibers from primary and secondary spindle receptors; longer duration effect than succinylcholine	Cat (69, 59, 58, 48)
Neostigmine	Increase in frequency of discharge in fibers from primary spindle endings. Antagonizes gallamine induced intrafusal n-m block	Cat (102) Frog (80)
Physostigmine	Increases effectiveness of fusimotor nerve stimulation; antagonizes intrafusal n-m block by tubocurarine	Cat (90) (55)
	Potentiates and prolongs spindle excitation induced by succinylcholine	Cat (21)
Edrophonium	Same effects as neostigmine but less potent	Cat (102)
Epinephrine Norepinephrine	Moderate increase in spindular afferent discharge followed by marked decrease in tonic discharge; increase in threshold to stretch.	Cat (49, 92, 122, 127) Frog (126b)
Atropine	Decrease in tonic afferent nerve discharge frequency, response to intrafusal fiber stimulation, and muscle twitch	Frog (138)
Caramiphen	Decrease in frequency of discharge of fibers from primary endings to tonic stretch; less decrease in response to phasic stretch	Cat (29)
Increase in Potassium	Tonic discharge frequency of spindle receptor afferent nerves elevated; alteration of temperature-response characteristics of spindle receptors	Cat (114) Frog
Hypocalcemia	Bursts of high frequency discharges in afferents from spindle stretch receptors	Cat (136)

mission (38) but this is also complicated by the concomitant increase in discharge frequency in afferent fibers (see below). The spontaneous contractions and action potentials observed with isolated frog muscle spindles (97) are abolished by tubocurarine (27). A decrease in frequency of potentials recorded from intracapsular sensory fibers after exposure to curare was also noted (see 80). However, in intact isolated frog muscle preparations very little change in tonic afferent discharge frequency is produced by neuromuscular blocking concentrations of tubocurarine (138).

The relative sensitivity of the extra- and intrafusal muscles to curariform agents with different frequencies of nerve stimulation has not been examined. Under many conditions the fusimotor system is tonically active, and the frequency of fusimotor nerve discharges is generally above that of *alpha* motoneurones (see 95). Thus, assuming that the relationship between frequency of nerve stimulation and degree of n–m block by tubocurarine were the same for both extra- and intrafusal fiber junctions, it would be expected that the intrafusal n–m transmission would be relatively more depressed in the intact animal by tubocurarine than the response to single nerve shocks. This follows since the magnitude of n–m block by tubocurarine and similar substances is increased with an elevation of the frequency of nerve stimulation. However, tubocurarine and four related *bis*-isoquinoliniums were not found to produce any more inhibition of the stretch reflex of decerebrate cats (in which fusimotor fibers are tonically active) than could be accounted for on the basis of extrafusal n–m block (138).

The assessment of drug action on the muscle spindle sensory ending and intrafusal muscle fibers is hampered by the complexity of the organ. Stimulation of the entire motor nerve results in contraction of both the intra- and the extrafusal muscle fibers with the consequent complication of the alteration in the length of the muscle. Functionally single fusimotor fibers can be isolated in ventral root or motor nerve filaments, but only a small proportion of the spindle endings can be activated by single shock stimulation of such fusimotor nerve fibers (56, 93). Single stimulation of the entire motor nerve in the presence of partial or complete extrafusal n–m blockade also results in a complex pattern of activation of some spindle endings (38, 71). Repetitive stimulation leads to a facilitation and an increase in the discharge frequency of both the primary and the secondary spindle endings (e.g., 38, 56, 93). The behavior of spindle endings to stimulation of fusimotor fibers led Hunt & Kuffler (93) to suggest that the intrafusal fibers, at least in part, might resemble the slow contracture muscles of the frog. Histological studies are consistent with this interpretation (7, 9, 15, 16, 17, 18, 20, 50) in that of the four to twelve intrafusal muscle fibers a portion are of distinctly smaller diameter, tend to have nuclei arranged in chains, appear to be more "fibrillar" in myofibril arrangement, may divide and re-unite, and receive a rather abundant diffuse small diameter motor nerve supply, the γ_2 fibers of Boyd (18). The larger fibers have "nuclear bags," are longer, tend to be less fibrillar, and receive a γ_1 motor innervation towards the end of each pole

consisting of discrete endplates (15, 16). This author suggested that these two fiber groups represent tonic and twitch fibers, respectively. In addition, differences in contraction and electrophysiological properties have been reported (16, 20). Barker and co-workers (9 to 11) emphasize that perhaps the distinction among fibers, at least histologically, cannot be made so strictly. Some fibers may appear areal (i.e., perhaps tonic) in one portion of the spindle, and fibrillar (i.e., perhaps twitch) in another portion (11). Barker (9) would recognize both the large and small fibers as distinct types but introduces a third, intermediate, type. Also, Barker & Cope (10) disagree with Boyd and state that neither the γ_1 nor γ_2 fibers are specific with respect to the fiber type they innervate.

Whether the intrafusal fibers can receive some innervation from *alpha* and/or *beta* motoneurons is an open question (see 19, 71, 131), but the innervation of the mammalian spindle by *alpha* collaterals of *alpha* motor nerves seems unlikely (9). In the frog, the distinction between intra- and extrafusal fibers is not so significant since the same nerve fiber may innervate both types (72).

In contrast to tubocurarine-like substances, SCh, ACh, and decamethonium produce a marked increase in the frequency of discharge of afferent fibers from mammalian primary and secondary spindle endings (Table I). Golgi tendon organs are unaffected (69). Granit *et al.* (69) concluded that the spindle afferent excitation was probably due to the action of these agents directly on the sensory ending since SCh was known to induce excitation of the carotid chemoreceptors (109). Hunt (90) suggested, on the other hand, that ACh acted upon the intrafusal muscle endplate to induce muscle contraction. Later investigations have shown that SCh fails to have mammalian spindle receptor stimulating effects after exposure of a muscle to ryanodine and repetitive nerve stimulation (139). The ryanodine presumably produces irreversible contracture of the intrafusal fibers in analogy with its known effect on extrafusal fibers. The response of the endings to stretch and an excess of potassium was not grossly altered at a time when no response to succinylcholine was obtained. Thus, it would appear that SCh, at least in small doses, induces excitation of the spindle receptors via activation of the intrafusal muscle fibers. However, some change in muscle receptor sensitivity might also be produced by ryanodine in view of the report of Ahmad & Lewis (1) that ryanodine produces an increase in calcium efflux and influx, increased release and decreased uptake of potassium, and an increase in sodium influx. The long-lasting effects of SCh infusions (21) or decamethonium (59) are consistent with the view that these agents produce a contracture of the intrafusal fibers on the assumption that at least a portion of these are slow contracture muscles.

Attempts to demonstrate directly that the mammalian intrafusal fibers are slow muscles capable of graded contractures have been generally unsuccessful. Koketsu & Nishi (105, 106) concluded that frog intrafusal fibers resembled twitch fibers more closely than slow fibers; Eyzaguirre (56) could

detect only propagated action potentials using extracellular recording from cat tenuissimus muscle. However, Eyzaguirre pointed out that perhaps non-propagated potentials might have been too small to be detected. Also, it is feasible that the intrafusal muscle fibers are analogous to the slow muscles of the birds, as pointed out by Diete-Spiff (38), in which a single fiber may respond with a propagated action potential or a local depolarization and contracture [Ginsborg (60)].

The demonstration of the sensitivity of small peripheral nerve fibers to ACh and similar substances (3 to 6, 41) raises the possibility that the fine, nonmyelinated terminals of a variety of nerve endings might be excited by such substances. However, Ottoson (121) found that ACh and SCh have, if anything, a depressant action directly on the afferent terminals of isolated frog muscle spindles whose intrafusal fibers had been destroyed in the process of dissection and mounting of the spindle. Transient increases in afferent discharge frequency followed by a decrease were observed with the non-quaternary anticholinesterases, eserine, di-isopropylfluorophosphate, or Mintacol.

It is generally implied that the effects of fusimotor stimulation on the afferent discharge are the consequence of shortening of the intrafusal muscles, but the possibility that some sort of electrical interaction between the propagated or electronically conducted end-plate potential and afferent terminals cannot be excluded, particularly in the consideration of the action of membrane depolarizing agents.

Spindles in isolated frog muscles are also activated by ACh and SCh (Table I); however, investigation of the site and mechanism of action in such preparations is severely compromised by the occurrence of marked tachyphylaxis (81, 138). There is a concomitant tachyphylaxis to the n–m blocking action of ACh (138).

The excitatory effects on the sensory discharge frequency of either SCh or ACh can be antagonized by tubocurarine or dihydro*beta*-erythroidine (Table I). This block can be overcome by increasing the dose of the agonist, as would be expected on the assumption that tubocurarine and the choline esters are competitive antagonists [see the recent study of Jenkinson (101) using twitch muscle fibers]. The observation that the spindle excitatory action of SCh can be obtained after doses of tubocurarine which block extrafusal and intrafusal n–m transmission has been cited as evidence that SCh acts directly on the sensory ending (81). However, this is not decisive since competition between SCh and tubocurarine could take place at either the afferent ending or the post-synaptic muscle membrane and would not necessarily involve a detectable change in n–m transmission.

The study of the action on muscle spindles of parenterally administered SCh and decamethonium is complicated by changes in blood potassium levels (104, 107, 125), and with large doses by the possibility of sympathetic ganglion stimulation (144).

Although it is hazardous to extrapolate values of ion levels in plasma to

tissue levels at specific sites of drug action, the magnitude of the potassium release after SCh might alone be sufficient to induce an appreciable change in spindle receptor function. For example, Klupp & Kraupp (104) reported a 30 per cent increase in blood potassium after 200 μg/kg of SCh intravenously; this dose produces moderate spindle excitation (21). A 50 per cent increase in the potassium concentration of Kreb's solution bathing an isolated cat tenuissimus muscle produce a marked increase in the spindle discharge frequency at temperatures between 32 and 39°C. (114). The magnitude of the potassium effect was a function of temperature. A maximum response was obtained at 34–36°C.

The response of the primary endings to stretch tends to be more phasic than that of the secondary (14, 33, 35, 38, 77, 98, 99); the anticipated differences in the responses of the two endings to the stimulatory effects of SCh, decamethonium, or activation of the different types of intrafusal fibers have not been reported yet.

Neostigmine, edrophonium, and galanthamine also produce an excitation of muscle spindle primary and secondary endings (102). This stimulatory effect is observed in de-efferented preparations in which there is no fusimotor nerve activity. If these substances act purely by inhibition of cholinesterase at intrafusal n–m junctions [the central portion of the spindle in the area of the primary sensory ending is devoid of cholinesterase (e.g., 89)] then they might be expected to produce no effect in the absence of nerve excitation. Edrophonium and neostigmine could act directly to produce effects similar to those of acetylcholine in analogy to their reported direct actions on extrafusal fibers (129); however, the doses employed by Kato *et al.* would be expected to produce only slight, if any, direct stimulatory effects. Galanthamine is not a quaternary ammonium compound and would not be expected to have appreciable direct stimulatory action. The rather slow onset of action of these substances favors the interpretation that they do, in fact, act via inhibition of cholinesterase. If so, they might increase the vascular ACh level, a possibility which seems unlikely, or they might cause accumulation of spontaneously released ACh at the intrafusal n–m junctions in sufficient concentration to induce intrafusal fiber shortening. The latter suggestion seems feasible if some intrafusal fibers do indeed respond to depolarization with a sustained contracture and the spontaneous ACh release is sufficient. Evidence that the ACh release might be adequate comes from the study of Granit, *et al.* (70) in which it was observed that gallamine produced a decrease in spindle stretch receptor sensitivity to the "long term effect of tendon taps" even in denervated preparations. These authors suggested that there was spontaneous intrafusal n–m activity which was increased by stretch and the effects of which could be blocked by gallamine administration. Furthermore, fusimotor nerve fibers might also exhibit repetitive antidromic discharges after SCh or the anticholinesterases as do the *alpha* motor nerve fibers (102).

The sensitivity of spindle stretch receptors can be altered by stimulation

of the lumbar sympathetic fibers (49, 92). The two independent studies are consistent in their description of a moderate increase in spindle receptor nerve discharge frequency concomitant with an increase in threshold to stretch (92), followed by a prolonged decrease in the tonic discharge rate as well as an increase in threshold. Tendon organs respond similarly (49). The administration of epinephrine or norepinephrine could reproduce the pattern of effects of sympathetic nerve stimulation in cat (49, 92, 122, 127) or isolated frog (126b) muscle spindle preparations. However, rather large doses (3 to 300 μg/kg intravenous) of the adrenergic amines are required to produce detectable changes in spindle function in comparison to maximum epinephrine blood levels of 5 μg/kg/min attained following optimal stimulation of both adrenals (e.g. 28). These changes in afferent activity induced by epinephrine could be closely correlated with concomitant alterations in the stretch reflex (127). Stretch reflexes and spindle activity are decreased markedly in rats with adrenal insufficiency (126a). In contrast to epinephrine, 5-hydroxytryptamine is without action on frog spindle preparations (126b).

The actions of epinephrine and sympathetic nerve stimulation have been attributed to the changes in muscle circulation (49, 122), but direct effects on the afferent terminals must also play a role since these agents have qualitatively similar effects on isolated frog muscle preparations (126b), and since the characteristic spindle response is obtained following stimulation of the sympathetic innervation of muscles devoid of circulation (92). The nuclear bag region of the spindle receives very small fibers which may be sympathetic (7, 9, 10). It seems not unlikely that the effects of epinephrine are a function of dose and are due to both direct and vascular actions. As Hunt (92) pointed out, the functional significance of this sympathetic control is difficult to ascertain; the changes in the responses to fusimotor nerve stimulation induced by sympathetic trunk stimulation are not marked.

Caramiphen has been noted to decrease the spindle stretch receptor activity, particularly in the tonic sustained discharges. This peripheral depressant effect is obtained with the same doses as are effective in depressing the tonic component of stretch reflex in decerebrate animals (29). This observation confirms the early postulates that this agent acts, at least in part, by depressing muscle proprioceptive function (57); in addition caramiphen also depresses the flexor reflex to nerve stimulation (12). A similar depressant action on spindle stretch receptor discharges has been observed with benzonatate ("Tessalon": H. D. Henatsch, personal communication); this agent inhibits the discharge of lung stretch receptors (12), an action which caramiphen also possesses (148). Bein & Bucher (12) explain these actions of both substances on the basis of their local anesthetic properties. Although the orders of potency of these and other compounds were similar for depression of lung receptor discharge and flexor reflex, their local anesthetic activities in a number of tests varied markedly.

Doses of atropine up to 2 mg/kg intravenously have no effects on the cat gastrocnemius muscle spindle primary stretch receptor discharge to tonic stretch or the response to fusimotor nerve stimulation (unpublished observations), although afferent spindle discharges from *in vitro* frog muscle preparations are decreased in frequency by relatively large concentrations (138).

Topical application of veratrine sensitizes frog muscle stretch receptors to phasic stretch, whereas the response to sustained stretch is decreased (100, 45). The decrease in the tonic discharge might be related to the nerve blocking effect of veratrine alkaloids (see 88).

Muscle receptors other than those of the spindle and tendon organs have not been investigated with respect to changes induced by drugs. The receptors giving rise to Group III fibers do not form a homogeneous group; some come from muscle spindles, some from pressure receptors and perhaps from "pain" receptors (13b, 123, 124). The receptors of nonmyelinated afferent fibers have been reported to be sensitive to pressure and to muscle ischemia plus contraction and pressure (13a); however, Iggo (96) found that muscle ischemia did not arouse a very high frequency discharge even when combined with intercurrent tetanus of the muscle in contrast to the responses obtained with local pressure, temperatures below 25°C. or greater than 41°, or local injection of 5 per cent NaCl. The endings of these small fibers were only slightly or not at all affected by stretch or contraction of the muscle.

Alterations in reflexes associated with changes in spindle functions.—The increase in spindle receptor activity induced by SCh or decamethonium is associated with marked changes in the behavior of *alpha* motoneurons. Tonic *alpha* motoneurons, that is those which respond to muscle stretch by sustained repetitive discharges, are activated by administration of SCh (58, 82), but reflex discharges may be markedly depressed by the addition of further muscle stretch. Phasic motoneurons, on the other hand, respond only infrequently following SCh; with superimposed muscle extension they may exhibit tonic discharges (78, 83, 84, 87). These investigators have pointed out that the type of reflex response of a given motoneuron (i.e. whether phasic or tonic) is dependent not only upon the inherent properties of the motoneuron but the magnitude of the central and peripheral "drive" to which it is subjected.

The depression of the patellar reflex of cats by doses of decamethonium that had no detectable effect upon the quadriceps twitch to nerve stimulation was clearly demonstrated shortly after its introduction (61, 62). In contrast, such selectivity of action on reflex activity could not be obtained using the phasic and tonic components of the gastrocnemius stretch reflex in decerebrate cats (142).

The monosynaptic reflex response elicited by stimulation of dorsal roots or muscle nerves is also depressed by SCh (58, 59, 83), decamethonium (48, 58, 59), edrophonium, neostigmine, or galanthamine (102). However, low doses of galanthamine produce an increase in the monosynaptic reflex. The actions of SCh and decamethonium are the results of their effects on the

muscle. They may be obtained in spinal, decerebrate, or anesthetized cats; intra-arterial injections are effective in doses which have little action when given intravenously; the effects are observed in lumbar de-efferented preparations but are abolished by de-afferentation (48, 59, 82, 84). The depression cannot be explained on the basis of occlusion of the shock stimulus and the high frequency afferent action potentials since the effect is observed on recording the monosynaptic response to stimulation of the central end of a sectioned synergic muscle nerve (58, 78).

Somewhat analogous effects have been observed in man. Small doses of SCh induce or accentuate ankle clonus in patients with multiple or lateral sclerosis and the procedure has been proposed as a diagnostic aid (22, 143). The tremor of patients with Parkinson's syndrome is increased whereas the tonic stretch reflex recorded electromyographically is depressed or abolished with doses which have no apparent effect upon extrafusal n–m transmission (143). The Hoffman and tendon reflexes are also depressed (22, 33).

Many processes must be involved in the reflex effects of the sustained excitation of the primary and secondary spindle stretch receptors; the possibility that excitation of other muscle endings might occur cannot be excluded. The problem is the quantitative assessment of the role of each of the known mechanisms in the responses observed. The increase in motor neuron activity following spindle afferent excitation seems clearly related to the physiological activation observed with muscle stretch, the myotatic stretch reflex. The reflex activation of motor neurons following SCh can be invoked to explain, at least in part, the transient, *coordinated* muscle contractions observed with rapid intravenous injections of SCh; concomitantly there is the well-known direct excitation of individual muscle fibers and n–m block [see the recent report of Wählin (147)].

The exaggeration of tremor and clonus by SCh might be the result of an increase in sensitivity of primary spindle receptors to stretch since an analogous increase in physiological tremor can be brought on by stretch (112, 113). Granit *et al.*, (69) demonstrated a marked increase in response to SCh spindle excitation with moderate increase in static muscle extension; a similar sensitization of some spindle endings to the phasic muscle stretch may be observed after administration of small doses of SCh (unpublished observations). Some of the many possible central mechanisms also involved have been discussed by Struppler *et al.* (143) in relation to theories of the genesis of tremor and clonus.

The depression of the monosynaptic responses to nerve shocks by SCh is not the result of activation of the secondary spindle endings which would be expected to produce flexor activity and under certain conditions inhibition of extensors [see (95)], since the monosynaptic reflex of flexor muscles is also depressed by this agent (58, 86).

The increase in recurrent Renshaw cell inhibitory activity consequent to the motor neuron excitation might play an important role; the presence of motor neuron inhibition is evidenced by the decrease in the motor neuron

pool potential elicited by antidromic ventral root shocks after SCh (58) and the antagonism of the SCh induced depression by strychnine (58) and dihydro*beta*erythroidine (58, 78, 86, 87). However, in many instances dihydro*beta*erythroidine did not abolish the motor neuron depression induced by SCh, and both groups of investigators therefore suggested that other factors may be involved. Dihydro*beta*erythroidine, in the doses used in the above studies, can markedly decrease the effectiveness of SCh on the muscle spindle receptors (140) although Fujimori & Eldred (58) state that no decrease in spindle receptor stimulating action of SCh was observed after dihydro*beta*erythroidine in their experiments. But the possibility of peripheral interaction makes it difficult to interpret the results obtained with this agent. Complete abolition of Renshaw cell activity by dihyro*beta*erythroidine is unlikely (43). Also, the frequency of motor neuron discharge may be altered after erythroidine thus changing the conditions for testing the magnitude of the monosynaptic reflex (87).

Succinylcholine still induces depression of the monosynaptic reflex response to single muscle nerve shocks after large doses (2 to 4 mg/kg intravenously) of dihydro*beta*erythroidine have been given solely into the circulation of the cord by means of cross circulation of the leg or occlusion of the abdominal aorta (140). Thus, other mechanisms than increased Renshaw cell inhibitory activity must play a role in the SCh induced monosynaptic reflex depression. Among those considered have been "subsynaptic depression" of the motor neuron by the sustained afferent input (143), the closely allied idea of occupation of motor neurons by this sustained input (86), as well as the "presynaptic inhibition" (78) emphasized recently (44 to 46). However, what role presynaptic inhibition of the type described by Eccles and co-workers might play in the depression of the monosynaptic reflex induced by SCh is not clear. This is so because the presynaptic inhibition and depolarization of central terminals of Group I afferent fibers induced by tetanic muscle nerve stimulation is most marked on stimulation of certain flexor muscles, whereas gastrocnemius muscle nerve stimulation has only slight effects (46). Yet the extensor triceps surae muscles have been the ones most used in the studies of the reflex depression following spindle stretch receptor excitation.

The effects of spindle stretch receptor excitation by SCh and decamethonium on the ventral root monosynaptic response appear analogous to the effects of static muscle stretch (91) or repetitive stimulation of Group I fibers [see (36)]. Hunt (91) found a consistent decrease in the magnitude of the monosynaptic response with static loading of the muscle adjusted so that receptor excitation was limited largely to muscle spindles and not Golgi tendon organs. In decerebrate preparations static loading sometimes produced facilitation of the reflex and with larger loads depression. Phasic muscle stretch of moderate degree, on the other hand, is associated with an increase in homonymous and synergic monosynaptic responses; larger magnitudes of stretch induce inhibition (63, 68, 74, 95). Similarly, Hunt (91)

observed that repetitive stimulation of fusimotor fibers, immediately at the end of which the test shock was given, generally produced facilitation.

Thus, it can be suggested that the sustained drug induced spindle receptor exictation produces reflex effects quite similar to those of static muscle stretch but with one major difference in that the magnitude of the receptor response may be much greater after the pharmacological stimulus than after muscle stretch. Therefore, small degrees of primary spindle stretch receptor excitation should be expected to produce facilitation in a certain percentage of the preparations; and, in fact, Kato *et al.* (102) have recently mentioned that small doses of SCh, edrophonium, or galanthamine may produce an increase in the monosynaptic reflex amplitude. Also, a transient increase in the Hoffman-reflex, followed by depression of triceps surae muscles of patients has been observed with SCh administration; this increase occurs only when the muscles are under external stretch (23).

However, the quantitative relationships between dose and among the various effects—excitation of primary and secondary spindle endings, block of intra- and extrafusal n–m transmission, changes in monosynaptic reflexes, degree and nature of activation of motor neurons and motor nerve fibers—are not definitively established. That some degree of specificity of action can be obtained is evidenced by the studies which show effects on reflex responses in doses which have no detectable extrafusal n–m actions. Even this type of investigation has its problems. Erdmann and co-workers (51) confirmed the observations that n–m blocking agents had an apparently selective depressant effect on reflexly induced muscle movements ("lissive action") and subsequently demonstrated (52) that this "lissive action" was due, at least in part, to the nonlinear relation between the mechanical response and intensity of nerve stimulation. A given dose of curare may produce a marked decrease in the response to submaximal nerve stimulation and only a slight effect on the response to maximal shocks. These studies emphasize the necessity of accurate assessments of the parameters of stimulation and response over the entire functionally significant range; the responses to electrical nerve stimulation do *not* necessarily run parallel to responses to natural nerve excitation!

Drug induced alterations in fusimotor outflow.—Matthews (116, 117), and Matthews & Rushworth (118 to 120) have demonstrated that a rather selective block of fusimotor (and smaller) fibers with little or no change in function of *alpha* nerve fibers can be obtained by the application of procaine to the muscle nerve. The technique has proved particularly useful in the study of the relations among fusimotor outflow, stretch receptor sensitivity to muscle stretch, and reflex responses. Procaine block of fusimotor fibers in decerebrate cats usually results in an elevation of the threshold but no change in the slope of the approximately linear relationship between tonic stretch reflex magnitude and soleus muscle extension. The sensitivity of the phasic stretch reflex is also reduced, but no systematic comparisons between the be-

havior of the phasic and of the tonic components of the reflex after procaine have been made.

Muscle tone and tendon reflexes in man are decreased in a similar fashion by application of procaine to peripheral nerves (130) or spinal roots (109b) at a time when only slight changes in maximum voluntary muscle strength occur. This decrease in muscle tone is observed in normal individuals as well as those with spasticity or rigidity. Both of these reports conclude, in analogy with experiments with cats, that the decrease in reflex activity is the result of partial block of fusimotor axons. However, Landau *et al.* (109b) have concisely emphasized that these experiments do not conclusively indicate that excessive fusimotor activity plays a major role in the pathophysiology of spasticity or rigidity in man. Also, it could be pointed out that the curves obtained by the last authors relating the decrease in reflex activity to maximal voluntary strength have the same characteristics as those relating the responses to maximal and sub-maximal nerve shocks with partial n-m block (52). A further complication of these experiments is the assessment of the effects of procaine on tonically discharging fibers as compared to those only phasically active.

The effects of general anesthetics have been investigated primarily in rats (2) and rabbits. Diete-Spiff and co-workers (39, 40) describe three types of activity of efferent nerves isolated from the muscle nerves of decerebrate rabbits; one of these was identified as *alpha* motor, and two presumptively as fusimotor. The more regularly discharging, Type I, fusimotor fiber with smaller amplitude potentials discharged more rapidly following administration of ether, ethyl chloride, trichlorethylene, or chloroform. The authors concluded that the fusimotor neuron excitation was not solely the consequence of respiratory tract irritation since it appeared most marked some minutes after the reflex coughing and movements at the start of inhalation; it was obtained in very deep anesthesia; it was also seen after large doses of thiopental; and the effect was observed after vagotomy. In contrast, firing of Type I fibers was decreased after chloralose, hexobarbital, and thiopental. The irregularly discharging, Type II, fusimotor fibers exhibited erratic responses to the above anesthetics whereas the discharge frequency was consistently elevated by intravenous administration of large doses of epinephrine (50 to 100 μg/kg) or vasopressin (5U).

Andrew (2) made similar observations in rats anesthetized with urethane. Trichlorethylene, ethyl chloride, chloroform, and ether increased tonic fusimotor nerve activity, but the reflex activation of the same units was depressed. Urethane, thiopental, and pentobarbital decreased both the tonic activity and reflex effects. Bromochlorotrifluoroethane and nitrous oxide depressed the reflex responses of the small motor nerve fibers but did not alter the resting firing frequency.

These excitatory effects of ether on fusimotor efferent neurons were absent in rabbits with sections at or below the level of the acoustic tubercles

(40). In contrast to observations in cats (24, 111, 132, 146), no spontaneous tonic fusimotor activity was found in these spinal rabbits although stimulation of skin or sural nerve set up fusimotor activity. Administration of ether or ethyl chloride to spinal preparations produced only depression of the reflexly evoked fusimotor activity. On the other hand, the tonic fusimotor neuron discharge, which could be obtained during and following electrical stimulation of the distal stump of the spinal cord, was increased by ether or ethyl chloride as in decerebrate or anesthetized preparations. The authors point out that ether, and ethyl chloride could act to facilitate conduction or transmission at many sites along the indirect polysynaptic pathways from the medulla to the fusimotor neurons. It seemed unlikely that the action of ether was solely on the fusimotor cells themselves since spinal reflex activation of the fusimotor neurons was depressed.

The depressant effects of barbiturates on fusimotor activity have been mentioned by a number of investigators (2, 25, 26, 39, 111, 137a, b). It was found that the facilitation of flexor and extensor fusimotor neuron activity, as detected by changes in spindle afferent discharge frequency in deafferented preparations, induced by stimulation of basal ganglia, hypothalamus or reticular formation was generally depressed by pentobarbital. However, in "moderate" and "deep" anesthesia (at unspecified times after 10 to 30 mg/kg pentobarbital intravenously or intraperitoneally) flexor spindle activity was increased by stimulation of the internal capsule, globus pallidus, or caudate nucleus, whereas extensor spindle activity was concomitantly decreased (137). The existence of two descending pathways to fusimotor neurons was postulated, a diffuse activating tonic system, and a reciprocal modulating pathway, somewhat similar to the earlier suggestion of Granit & Holmgren (67).

A decrease in fusimotor neuron activity has been observed after mephenesin administration. Hunt & Paintal (94) reported a depression in spontaneous activity. An increase in the latency and a transient blockade of rabbit muscle spindle afferent nerve response initiated by stimulation of the mesencephalic tegmentum was observed by Granit & Holmgren (67); and it was concluded that mephenesin acted on a "fast" polysynaptic pathway from the mesencephalic tegmentum to the fusimotor ventral horn cell. The possibility of a direct depressant effect of mephenesin on the spindle was also mentioned by Granit & Holmgren; this observation is pertinent to the consideration of the mechanism underlying the muscle relaxant actions of this substance and needs further investigation. These effects of mephenesin are not unexpected in view of the depressant action of this compound on a variety of neural processes, in particular those involving repetitive activity (115), posttetanic potentiation or both (65, 110).

Chlorpromazine (79), as well as acetopromazine and meprobamate (24), are strikingly effective in depressing the sustained spontaneous and reflexly induced fusimotor neuron activity in decerebrate cats. This observation provides an appropriate explanation for the abolition by chlorpromazine of

the rigidity induced by intercollicular section, and its much less marked effects on the rigidity of "anemic" decerebrate preparations (79). In intercollicularly decerebrate preparations chlorpromazine also induces a decrease in the segmental monosynaptic reflex, and a somewhat less marked decrease of polysynaptic reflex potentials (79, 108), a depression of posttetanic potentiation of single motor neuron unit response to muscle stretch, but no change in the posttetanic potentiation of the monosynaptic reflex elicited by repetitive electric shock conditioning of the muscle nerve (79). The low doses of chlorpromazine which alter fusimotor neuron activity have been generally found to have little effect in spinal preparations (128); however, Schulte & Henatsch (132), and Busch *et al.* (24) noted that the tonic activity of *alpha* or *gamma* motor neurons, which could be observed in spinal animals or be induced reflexly, was also promptly abolished by chorpromazine. DeSalva & Ercoli (37) mention that the depression of contralateral facilitation of the knee jerk by chlorpromazine was significantly greater in decerebrate than in spinal cats. The presence of effects on central functions other than those directly involved in efferent fusimotor activity precludes the assigning of a specific action of chlorpromazine on the fusimotor system or the reticular formation as had been suggested (24, 79).

The tonic discharges of *alpha* motor neurons to muscle stretch are converted to a phasic response after the phenothiazines, meprobamate, and a benzodioxane derivative (24, 85). However, a more marked depression of the tonic component of the stretch reflex than of the phasic has been observed with a variety of central nervous system depressants including pentobarbital (29). Although the change to stretch from a tonic to a solely phasic reflex response may be the result of a diminution of sustained fusimotor activity, this shift in reflex response character may be relatively nonspecific. For example, the greatest depression of the tonic component of the stretch reflex as compared to the phasic was obtained with mephenesin, caramiphen, and scopolamine, agents which probably have different sites or modes of action or both (29).

Suppression of fusimotor neuron tonic activity, and responses to central activating stimuli have also been observed with a benzodioxane derivative(2-(γ-methoxypropylaminoethyl)-1,4-benzodioxane hydrochloride) (85). This agent, however, is a relatively strong adrenolytic substance and also depresses monosynaptic reflex responses in decerebrate, anesthetized, and spinal animals; it has no effect on or may actually increase posttetanic potentiation.

Lumbar fusimotor neuron activity of cats is increased by asphyxia, hypoxia, or a fall in blood pressure, but is unaffected by hypercapnia (146). This investigator also noted that epinephrine (1 to 2 μg/kg intravenously) produced a temporary increase in fusimotor discharge frequency [see also (39)] which could be abolished by complete isolation of the cord segment by section of the cord and dorsal roots. No change was observed after norepinephrine (1 to 10 μg/kg) or serotonin (2 to 40 μg/kg) intravenously admin-

istered; however, the latter had an excitatory effect when applied topically on the spinal cord. Activation of baroreceptors of the carotid sinus is inhibitory to lumbar fusimotor neuron activity (133), whereas fusimotor activation is induced by distention of the carotid or stimulation of the carotid chemoreceptors by oxygen lack or cyanide (134).

The major problem in the interpretation of the pharmacologically induced changes in muscle and muscle spindle function is the quantitative assessment of the nature of the changes induced in various portions of the central and peripheral system involved. This requires definitive experiments on the effects of drugs on each portion of the system, and this necessarily should include a description of the dose-response and stimulus relationships; none of the agents described above have received such intensive study. In addition, it should be emphasized that statements of site of action can only be made when the agent has its expected effect on an isolated portion of system under study; when it does not it cannot be concluded, *pari passu*, that the action is on the portion excluded from study. An excellent example has been cited above in which ether and other anesthetics evoke an increase in fusimotor activity; this activation was not seen in spinal animals, thus suggesting that the agents act primarily on the nervous system above the level of the section. However, if the stump of the cord was stimulated repetitively, the ether administration again produced the typical activation of the fusimotor neurons!

Further systematic experimentation is required before a rational synthesis can be presented describing the relationships among the peripheral and central motor systems, the alterations produced by drugs, the interactions among the component systems, and the correlations among neuronal components affected, dose employed, and the end change in muscle function. The study of the specificity of the fusimotor control system(s) in motor regulation (see 99) and in learning (25, 26) provides fascinating prospects for future investigations.

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