Factors altering crossed extensor reflex excitability in decerebrate cats : relation of reflex response to pain summative mechanisms
by Mark J Koebbe

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science of Biological Sciences
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Abstract:
The crossed extensor reflex (CER) evoked in decerebrate cats has been classically described as a labile response recruited by the production of the flexor withdrawal reflex (FR) in the ipsilateral limb. Although the two reflexes, the FR and the CER, are related, the CER is more susceptible to a variety of different sensory inputs and shows different characteristics of reflex recruitment. This report provides evidence that the CER in decerebrate preparations may not be as labile as has been previously reported and in addition may recruit activity in a similar manner to the flexion reflex.

Eleven cats were decerebrated at the intercollicular level of the brainstem under ether anesthesia. CERs in the right quadriceps muscle were evoked by stimulation through indwelling electrodes in the left sciatic nerve and inhibited by stimulation of the right sciatic nerve. The CERs were monitored by recordings of isometric tension in the right quadriceps muscle.

CERs in the right quadriceps could be evoked by a single stimulus of the left sciatic nerve under certain prerequisite conditions. The excitability of the CER evoked in the right quadriceps was altered by rotation of the body from side to side (body position), head rotation, mechanoreception, and flexion of the left forelimb.

With the decerebrate cats in an appropriate position to evoke consistent CERs, CERs exhibited several features of recruitment indicative of prolonged central summation. Very low frequencies of stimulation evoked summation of the CER. This is consistent with properties of "windup" observed in the recruitment of the FR, discharges of certain populations of dorsal horn intemeurons, and the perception of noxious stimuli.

These results point out that the excitability of a classical segmental reflex, the CER, are highly affected by descending influences from supraspinal and suprasegmental inputs related to static righting and postural reflexes. Features of the recruitment of the CER suggest that sensory recruitment and reflex recruitment may involve similar mechanisms in certain conditions, although some differences in the duration of the summation of the CER may reflect the modulation by descending and intersegmental inputs.

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ABSTRACT

The crossed extensor reflex (CER) evoked in decerebrate cats has been classically described as a labile response recruited by the production of the flexor withdrawal reflex (FR) in the ipsilateral limb. Although the two reflexes, the FR and the CER, are related, the CER is more susceptible to a variety of different sensory inputs and shows different characteristics of reflex recruitment. This report provides evidence that the CER in decerebrate preparations may not be as labile as has been previously reported and in addition may recruit activity in a similar manner to the flexion reflex.

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These results point out that the excitability of a classical segmental reflex, the CER, are highly affected by descending influences from supraspinal and suprasegmental inputs related to static righting and postural reflexes. Features of the recruitment of the CER suggest that sensory recruitment and reflex recruitment may involve similar mechanisms in certain conditions, although some differences in the duration of the summation of the CER may reflect the modulation by descending and intersegmental inputs.

INTRODUCTION TO THE PRESENT STUDY

The following study is an examination of different sensory inputs which alter the excitability of the crossed extensor reflex (CER). Although previous studies have indicated that the CER is a much more inconsistent (labile) reflex than the flexion reflex (FR) (Creed et al., 1932), the experiments presented are an extension of a serendipitous observation that the rotation of a decerebrate preparation onto its right side, evoked by iterative stimulation of the left sciatic nerve, coincided with a consistent increase in the excitability of the CER recorded from the right quadriceps muscle. In this new position (with the animal on its right side) even a single stimulus of the left sciatic nerve evoked a CER. No previous reports had indicated this degree of excitability of CERs in decerebrate animals (Eccles and Granit, 1929; Pi-Suner and Fulton, 1929).

Since the changes in excitability of the CER were paralleled by postural movements of the entire animal, subsequent experimental manipulations were designed to examine the relationship of the CER to postural and static righting reflexes. These relationships were examined by changing whole body position, rotating the head to either side, flexing or extending the forelimbs, and placement of an opposing surface against the left side when the animal was placed on its right side.

The results of these experiments are considered with respect to previous studies which had indicated an increase in the excitability of the CER in acute decerebrate animals, but only with certain manipulations (or stimulation) (Beritoff, 1915; Perl, 1957; Pi-Suner and Fulton, 1929) or further surgical modifications of the decerebrate preparation (Eccles and Granit, 1929; Forbes and Cattell, 1924; Matthes and Ruch, 1933; Rossignol and Gauthier, 1980).

Although both the flexor withdrawal (FR) and crossed extensor reflexes have been classically related to behavioural responses evoked by noxious stimulation (Sherrington, 1910), previous studies have primarily used the flexion reflex to examine recruitment of nocifensive reflexes (Willis, 1982). Until the present study which describes CERs evoked by single stimuli, the CER has proven too labile to study recruitment evoked by low frequency stimulation.

Several recent studies have indicated that recruitment of the late flexor withdrawal reflex which is evoked by noxious stimulation of C afferents is dependent on the frequency of stimulation of these afferents (Iwamoto et al., 1980; Price, 1972; Schouenborg and Sjolund, 1983). These studies have indicated a relationship between the summation of activity in dorsal horn interneurons and perception of pain, as well as, recruitment in nocifensive reflex paths. For this reason the second part of the study used similar low frequencies of stimulation to evoke summation in the CER. The ability of the CER to recruit activity in the central nervous system is considered with respect to the previously mentioned studies of spinal cord summation.

REVIEW OF THE LITERATURE

The flexor withdrawal and crossed extensor reflexes have been described as parts of a coordinated behavioral response to noxious or painful stimulation (Sherrington, 1910). The flexor withdrawal reflex is the predominant nocifensive response to noxious stimulation of a limb or to direct stimulation of nociceptive afferent nerves in that limb. Ipsilateral flexion of the whole limb can be evoked by stimulation of a focal area on the limb. Flexion of the entire limb involves recruitment of synergistic flexor muscles. Extension in the contralateral limb, the crossed extension reflex (CER), also requires recruitment originating from the ipsilateral withdrawn limb.

Current texts of medical physiology retain this classical interpretation of the relationship between the flexion reflex (FR) and the reciprocal response of the crossed extension reflex (CER) (Mountcastle, 1980). The FR and CER continue to be considered as congruent aversive responses to noxious stimulation. Flexion withdrawal of one limb is accompanied by extension of the contralateral limb to prevent a loss of equilibrium.

Reflexive (involuntary) and motivated motor responses make use of a common pool of motorneurons, "the final common path" (Sherrington, 1906a). Sherrington and colleagues (summarized in Creed et al., 1932) demonstrated that the nature of an evoked reflex is influenced by various weighted afferent and central nervous inputs to the spinal cord motorneurons. For example, acute decerebrate preparations exhibit a pronounced tonic rigidity in extensor (antigravity) muscles (Sherrington, 1898). This rigidity is abolished or diminished by deafferentation (Sherrington, 1898; Denny-Brown, 1929) and by transection of the spinal cord (Liddell et al., 1932b). These findings point out the importance of both afferent and brainstem mechanisms in producing this tonic facilitation in extensor muscles.

Although there are some differences in the characteristics of the flexion withdrawal reflex and the CER, many studies show a strong relationship between the nocifensive FR and the CER. Historically, the CER is described as an "associated" nocifensive reflex which results from a radiation or recruitment of the flexor withdrawal reflex (Sherrington, 1910). More recent studies, recording ventral root reflexes evoked by stimulation of afferent nerve fibers, show a direct association between polysynaptic flexion reflexes and crossed extensor responses (Holmqvist, 1961; Jankowska et al., 1967a).

The FR is more traditionally used as a model of nocifensive responses than the CER. This may be a result of the more labile nature of the CER (Creed et al., 1932; Holmqvist, 1961). The CER in decerebrate cats is not an unequivocable response. The unpredictable nature of the CER in decerebrate cats may be a result of tonic brainstem inhibition and/or variability incurred by the crossed cord path (involvement of more interneurons). For instance, only one known study has reported that CERs can consistently be evoked by single stimuli in otherwise intact acute decerebrate cats (McMillan and Koebbe, 1981). This was seen only under appropriate conditions of body and head position.

Classical Consideration of Different Types of Flexor Reflexes.

Early work with flexor reflexes alluded to differences between the reflex evoked by noxious stimulation (withdrawal) and that associated with innocuous inputs (pluck reflex) (Sherrington, 1910). The types of spinal reflexes evoked depended on the local sign of the stimulus (where the stimulus was applied) (Sherrington, 1903; Sherrington, 1906b) as well as the quality of the stimulus (Graham-Brown and Sherrington, 1912; Sherrington, 1910).

Some major differences have been noted between the withdrawal types of flexor reflexes and flexions evoked by innocuous stimulation (Creed et al., 1932). The flexor withdrawal reflex which is evoked by noxious stimulation radiates to incorporate other synergistic flexor muscles and even to the opposite side of the cord where it recruits the CER (Sherrington, 1906a; Sherrington, 1910). Maintained noxious stimulation can also recruit responses in the fore- and hindlimbs simultaneously (Sherrington, 1910). Flexor or extensor reflexes are also evoked by innocuous stimulation of cutaneous afferents from the surface of the skin overlying the muscle (Hagbarth, 1953). Although such reflexes may be evoked by a vigorous pinch, this response does not radiate to synergistic muscles and is confined to the muscles at one joint.

The ability of nocifensive reflexes to recruit activity in more than one muscle is apparent in the classically described properties of reflex fractionation, subliminal fringe, and occlusion. Maximal stimulation of a single afferent nerve evokes responses in only a fraction of the motor units to a given muscle. Activation of many afferents may be required to evoke a maximal reflex in that muscle (Cooper et al., 1926). Two weak stimuli given simultaneously to an afferent nerve, each which is incapable of evoking a response individually, may sum temporally to produce a response. This result indicates that motorneurons may be activated subliminally by single stimuli. The combination of two or more such weak stimuli may sum to recruit motorneurons from this subliminal fringe (Eccles and Sherrington, 1930; Denny-Brown and Sherrington, 1928). In occlusion the flexion reflex evoked by simultaneous stimulation of the two afferents is less than the sum of the two responses to stimulation of the individual afferents (Cooper et al., 1927). All of these characteristics of nocifensive reflexes indicate that central processing of afferent information is required (Liddell and Sherrington, 1923b; 1925). Such central processing is responsible for recruiting responses from other synergistic muscles.

Early studies also emphasized the dominance of the FR relative to other reflexes (Graham-Brown and Sherrington, 1912; Sherrington, 1903; Sherrington, 1910). Reflexes such as the ipsilateral extensor reflex (Phillipson′s reflex) or the scratch reflex (Sherrington, 1906b), evoked by innocuous stimulation of skin, can be superceded by noxious stimulation of skin which evokes an ipsilateral flexion reflex.

Withdrawal reflexes persist for a longer duration than can be accounted for by the arrival of the afferent volley at the spinal cord (Creed et al., 1932; Sherrington, 1921). This afterdischarge in motor nerves was considered an indication of a facilitation mediated by elements within the spinal cord, reflecting a prolonged central excitatory state (Creed et al., 1932; Liddell and Sherrington, 1923b; 1925). This was demonstrated by using paired stimuli. The response evoked by a second stimulus was always larger and longer in duration than when the response was evoked by a single stimulus. The facilitation of the FR evoked by a single stimulus was dependent on the interval between the first and second stimuli (Sherrington, 1921). Protracted activity in the FR or CER evoked by iterative stimulation (Eccles and Granit, 1929; Liddell and Sherrington, 1923a) indicated prolonged central summation. Excitatory afterdischarges of the FR persist after removing all but one dorsal root. This result demonstrated that the prolonged responses were due to central excitatory processes rather than reiterative excitation by inputs from adjacent dorsal roots (Eccles and Sherrington, 1930).

Relation of Quality of Afferent Input to Flexion Reflexes.

Work in the 1930's began to distinguish differences in the function of different sizes of afferent fibers (Bishop and Heinbecker, 1935). Since noxious input was believed a prerequisite to the withdrawal, or flexor, reflex some investigators suggested a relationship between conduction in both the small myelinated (A-delta) and the unmyelinated (C) fibers, and the flexion reflex (Zotterman, 1939). Later studies demonstrated that small myelinated, or A-delta, and unmyelinated, or C, afferent fibers did indeed respond to noxious stimulation (Burgess and Perl, 1969; Bessou and Perl, 1967).

Recent studies question the strict relationship between conduction in small afferents, pain, and flexor reflexes. Small afferents can respond to innocuous mechanoreceptive and thermoreceptive stimuli as well as noxious stimulation (Kumazawa and Perl, 1977). Furthermore, group II and III muscle afferents, as well as cutaneous afferents of all sizes, can elicit flexor reflex discharges in ventral roots (Holmqvist and Lundberg, 1961; Holmqvist, 1961). The ability of qualitatively different afferents to evoke flexor reflex responses led Lundberg and colleagues to classify these afferents as flexor reflex afferents (FRAs) (Eccles and Lundberg, 1959; Holmqvist and Lundberg, 1961). Stimulation of high threshold muscle afferents (group II and III), joint afferents, and cutaneous afferents may all evoke flexor responses. While this classification system includes all afferents which can evoke a flexor response into one group, it fails to take into account differences in the qualitative and quantitative aspects of the flexor reflexes evoked by the different classes of afferents.

The relative contributions of different groups of afferent fibers to the FR was clarified by the classic studies of Lloyd in the 1940's (Lloyd, 1943a; 1943b; 1943c). First, he described short and long latency responses related to conduction in large and small myelinated afferents respectively. The early monosynaptic discharge was conclusively associated with activation of the large Ia muscle afferents (Lloyd 1943a; 1946). Polysynaptic reflex discharges with longer latencies were associated with inputs from cutaneous and high threshold muscle afferents (Lloyd 1943a; Lloyd 1943b). These results suggested that there are significant differences in the flexor reflexes evoked by the several classes of afferents capable of evoking flexor reflexes. The polysynaptic discharges evoked by larger afferents are brief (about 10 ms) (Lloyd, 1943a). Addition of A-delta (small myelinated) afferents to the afferent volley (stimulus) adds to the duration and the amplitude of the polysynaptic flexor reflex (Lloyd, 1943a; Lloyd, 1943b). Stimulation of unmyelinated fibers also elicits a delayed and prolonged flexor reflex discharge (Burke et al., 1971; Iwamoto et al., 1980; Koll et al., 1961; Price, 1972; Schouenborg and Sjolund, 1983). These prolonged discharges associated with input over high threshold (pain) fibers are more consistent with the magnitude and duration of the flexor withdrawal reflex than of flexor reflexes evoked by innocuous stimulation (Brooks and Koizumi, 1953; Iwamoto et al., 1980; Schouenborg and Sjolund, 1983).

The dependence of reflex response on the quality of afferent input is clearly evidenced by the reversal of reflex patterns under appropriate conditions. Stimulation of low threshold afferents evokes a crossed flexor reflex rather than a crossed extensor reflex (Perl, 1957; 1958). Similar low threshold inputs from large muscle afferents evoked by stretching muscle in the contralateral limb inhibit the CER evoked in that limb (Perl, 1959). These findings support classical studies which show that reflexes evoked by innocuous (low threshold) cutaneous stimuli may depend on the location of the stimulus (local sign) (Hagbarth, 1953; Sherrington, 1910). For example, bilateral flexion of the hindlimbs may be evoked by stimulation of cutaneous afferents of the hindlimb. Crossed flexor reflexes revert to crossed extension when high threshold cutaneous afferents are stimulated (Perl, 1957). This observation shows the ability of nocifensive responses to supercede reflexes evoked by low threshold stimulation (Sherrington, 1910).

Reflex reversal has recently been related to limb position (Grillner and Rossignol, 1978), and especially to limb position during the walking cycle (Rossignol and Gauthier, 1980). Stimulation of high threshold afferents evokes a crossed flexion reflex when the contralateral limb is extended during the swing phase of the walking cycle (Grillner and Rossignol, 1978). A further examination of this reflex reversal demonstrates that some afferents from muscles and/or joints in the extended limb are required to be intact (Rossignol and Gauthier, 1980). By progressively deafferenting the crossed limb these authors showed that almost complete deafferentation was required to abolish the crossed flexor response. This result is consistent with the importance of low threshold proprioceptive inputs to the limb in which the crossed reflex is evoked (Perl, 1959). CERs evoked by high threshold stimulation after deafferentation of the responding limb are larger than CERs evoked before the limb was deafferented (Rossignol and Gauthier, 1980). This is also consistent with earlier studies which described an increase in the excitability of the CER after deafferentation (Forbes and Cattell, 1924; Eccles and Granit, 1929; Pi-Suner and Fulton, 1929).

Convergence of Afferent Input to the Spinal Cord.

Since flexor reflexes can be evoked by stimulation of several classes of afferents (the FRAs), some authors have suggested that there is a convergence from FRAs onto a common flexor reflex pathway (Holmqvist and Lundberg, 1961). Support for convergence of afferent inputs onto common pathways comes from anatomical studies describing the cellular architecture of the dorsal and ventral horn of the spinal cord (Ralston, 1968a; 1968b; Rethelyi and Szentagothai, 1973; Szentagothai, 1964; Wall, 1967). Recordings from interneurons in the dorsal and ventral horns of the spinal cord also reveal that stimulation of qualitatively different afferent nerves can evoke discharges in single neurons (Kolmodin, 1957; Kolmodin and Skoglund, 1954; Kolmodin and Skoglund, 1960; Price and Mayer, 1974; Price and Wagman, 1970; Wagman and Price, 1969). Additional support for the existence of common paths comes from studies on the presynaptic control of afferent input (or sensory information) evoked by stimulation of different classes of afferent nerves (Mendell and Wall, 1964; Melzack and Wall, 1965).

Anatomical studies have shown that different classes of afferents terminate in different laminae of the spinal cord. The large muscular afferents (Ia and Ib) terminate in more ventral and medial laminae of the spinal cord (Scheibel and Scheibel, 1969; Brown, 1981). The cutaneous afferents, however, project to the dorsal horn (Brown, 1982). Large cutaneous afferents which originate primarily from mechanoreceptors activated by innocuous stimuli synapse primarily in laminae 3-5 of the dorsal horn (rev. in Brown, 1981). In contrast to the projection of large cutaneous afferents, the small myelinated (A-delta) and unmyelinated (C) afferent fibers synapse only in the first two laminae of the dorsal horn (Kumazawa and Perl, 1978; Light and Perl, 1979; Brown, 1982). Small myelinated afferents, A-delta, which are activated by noxious stimulation (Burgess and Perl, 1967; Christenson and Perl, 1970) terminate in the marginal zone, or lamina 1 (Kumazawa and Perl, 1978), while axons from the unmyelinated (C) afferents project largely to interneurons of the substantia gelatinosa (SG), or laminae 2 (of Rexed) (Light and Perl, 1979). These anatomical studies suggest specific differences in the projection of innocuous and noxious inputs to dorsal horn neurons.

Some of the anatomical features of dorsal horn interneurons further indicate the functional separation of noxious and innocuous afferent input. Many of the interneurons in laminae 3 and 4 make no apparent connections with interneurons in laminae 1 and 2 (Brown, 1981). The structure of many laminae 1 and 2 neurons indicates that these cells are largely confined to the lamina in which their cell bodies are located (Light et al., 1979; Price et al., 1979). These results show that interneurons in the different laminae may have specific sensory functions. However, some interneurons in the more ventral laminae of the dorsal horn (lamina 3) may send long dendrites into laminae 1 and 2 (Mannen and Suguira, 1976). These results suggest that different interneurons within the same laminae may respond to specific sensory inputs or may receive convergent inputs from interneurons in more dorsal laminae.

In contrast to the dorsal horn, the anatomical structure of the ventral horn of the spinal cord is considerably more complex. Terminals from long descending tracts, dorsal horn interneurons, and larger afferent collaterals contribute to the extreme complexity of the ventral horn (Rethelyi and Szentagothai, 1973; Wall, 1967). Rethelyi and Szentagothai (1973) have suggested that the ventral horn is a structural homologue of the reticular formation of the brainstem. The convergence of dorsal horn inputs onto interneurons of the ventral laminae of the spinal cord led Wall (1967) to describe a model of cascading inputs. The model basically proposed that interneurons in more dorsal laminae project onto neurons in a more ventral location. Although the anatomical studies described above indicate a functional separation between some laminae of the spinal cord, physiological studies show that ventral horn interneurons respond to a wide variety of converging inputs (Baldissera et al., 1981).

Pioneering studies on the physiology of spinal cord interneurons by Kolmodin and colleagues (Kolmodin, 1957; Kolmodin and Skoglund, 1954; Kolmodin and Skoglund, 1960) first indicated the existence of different functional classes of interneurons located in the dorsal horn (Kolmodin and Skoglund, 1960). Different interneurons were excited by noxious or innocuous stimulation of the foot pads in cats. These investigations also described neurons which were excited by noxious stimulation and inhibited by innocuous stimulation. These early studies showed that some interneurons responded specifically to noxious or innocuous stimulation, while some interneurons received convergent inputs from both noxious and innocuous inputs.

Recent studies describe such interneurons in more specific terms These studies describe different functional classes of dorsal horn interneurons. Although these studies use different classification systems, they all indicate the existence of three classes of interneurons in the dorsal horn (Chung et al., 1979; Price et al., 1979; Wall et al., 1979). Class 1 interneurons are specifically excited by innocuous stimulation, while class 3 neurons are only excited by noxious stimulation. Class 2 neurons which are excited by both innocuous and noxious stimuli have been described as wide dynamic range neurons in previous reports (Price and Mayer, 1974). Such wide dynamic neurons respond more vigorously when excited by noxious stimulation.

Brown (1982) has suggested that class 1 type neurons represent interneurons in laminae 3 and 4 which receive a predominate input from innocuous mechanoreceptors. Class 3 neurons excited only by noxious inputs are represented by interneurons of the marginal zone or the SG. Interneurons at the border of the substantia gelatinosa (lamina 2) and lamina 3, between the neurons responding to noxious or innocuous inputs, may be the wide dynamic interneurons described in earlier studies (Wall et al., 1979).

Cervero et al., (1979a; 1979b) describe a different group of dorsal horn interneurons which exhibit inverse patterns of responses. In contrast to class 3 interneurons, class 3 inverse neurons are only inhibited by noxious inputs. Class 1 inverse neurons are only inhibited by innocuous stimulation, while class 2 inverse neurons, or inverse wide dynamic range neurons, are inhibited by both innocuous and noxious inputs. These results suggest a complementary function for different populations of spinal cord interneurons.

The quantity and quality of afferent input to the spinal cord is regulated by presynaptic inhibition (Schmidt, 1973) or presynaptic facilitation (Mendell, 1972; Mendell and Wall, 1964) in which there is a depolarization or hyperpolarization of the terminals of primary afferents (Eccles et al., 1961; Eccles et al., 1962a; 1962b; 1962c; Mendell and Wall, 1964; Melzack and Wall, 1965). Wall (1962) mapped field potentials within the spinal cord evoked by primary afferent stimulation and identified the substantia gelatinosa as the region of the spinal cord where presynaptic inhibition occurs. A predominance of axoaxonic synapses in the SG has also been associated with presynaptic inhibition within the SG (Ralston, 1968a; Szentagothai, 1964). Primary afferent depolarization (PAD) results in a decrease in the synaptic efficacy of the stimulated primary afferents (Eccles et al., 1961; Eccles et al., 1962b). In contrast to PAD, primary afferent hyperpolarization evoked by stimulation of high threshold afferents may facilitate primary afferent input (Mendell, 1970; Mendell, 1972; Mendell and Wall, 1964; Melzack and Wall, 1965).

Although most reports indicate that PAD (or presynaptic inhibition) is confined to the primary afferents stimulated (Eccles et al., 1962a; Eccles et al., 1963a; 1963b), PAD may be evoked in terminals of different primary afferents under certain conditions (Jankowska et al., 1967a; Anden et al., 1966a; 1966b; Lund et al., 1965; Eccles and Lundberg, 1959). Stimulation of Ia afferents in spinal cats evokes PAD in FRA terminals (Lund et al., 1965).

Stimulation of FRAs can evoke an even larger PAD in the terminals of larger afferents (Ia) if DOPA is administered to acute spinal cats (Anden et al., 1966a; Jankowska et al., 1967a). The effect of DOPA on spinal neurons appears to involve one or more monoaminergic transmitters released by stimulation of different descending paths from the brainstem reticular formation (Engberg et al., 1968c; Krnjevic, 1981). The PAD evoked in FRA terminals by stimulation of Ia afferents of spinal animals is substantially smaller than the PAD evoked by Ia afferent stimulation in decerebrate animals (Eccles and Lundberg, 1959; Lundberg, 1982). These results indicate a reciprocal interaction of PAD evoked in large and small afferents. This reciprocal organization may involve the activation of different pools of interneurons which feedback upon specific terminals of different primary afferents (Eccles et al., 1962a; Eccles et al., 1963a; 1963b; Lundberg, 1982).

Other reports suggest that primary afferent hyperpolarization (PAH) results when high threshold FRAs (unmyelinated C afferents) are stimulated (Mendell and Wall, 1964; Melzack and Wall, 1965; Mendell, 1970; Mendell, 1972). These authors suggest that such hyperpolarizations facilitate primary afferent input to spinal cord interneurons (presynaptic facilitation). Earlier experiments had indeed shown that artificial hyperpolarization of the spinal cord facilitates afferent input and reflex activity (Eccles and Krnjevic, 1959; Eccles et al., 1962c; Wall, 1958). These results suggest that hyperpolarization evoked by stimulation of high threshold afferents may concurrently facilitate sensory inputs as well as reflex responses.

Presynaptic inhibition (PAD) and presynaptic facilitation (PAH) have been implicated as mechanisms involved in the gating or modulation of sensory (pain) information in the spinal cord (Melzack and Wall, 1965). In this scheme, common interneurons of the SG either facilitate transmission or inhibit transmission of primary afferent input to higher sensory receiving areas. Subsequent studies, however, have reported only PAD when high threshold afferents (unmyelinated) are stimulated (Burke et al., 1971; Schmidt, 1973). These results suggest that the SG is involved in gating sensory inputs to more ventral laminae of the spinal cord, although presynaptic effects may not alone account for this regulation. Further studies suggest that the duration of responses evoked in dorsal horn cells by stimulation of A-delta or C afferent nerves is more consistent with postsynaptic mechanisms of inhibition or facilitation (Price and Wagman, 1970; Price et al., 1971; Price, 1972).

Physiological analyses of responses of dorsal horn neurons evoked by large and small afferent fibers indicate a convergence of activity from these afferents on dorsal horn neurons (Mendell, 1966; Price and Wagman, 1970; Price et al., 1971; Price et al., 1978; Wagman and Price, 1969). Stimulation of large afferents alone evokes brief discharges followed by an inhibitory period (depressed background activity) (Price and Wagman, 1970; Wagman and Price, 1969). The duration of this inhibitory period (200-300 ms) is consistent with the duration of PAD (Price et al., 1971). If A-delta afferents are included in the afferent volley, a delayed and prolonged discharge follows the inhibitory period. Stimulation of unmyelinated afferents also evokes a prolonged response which can be augmented by low frequencies of stimulation (0.33 hz.) (Mendell, 1966; Price and Wagman, 1970; Wagman and Price, 1969). This recruitment of excitatory activity with succeeding stimuli has been termed "windup" (Mendell, 1966; Price, 1972). The relatively prolonged durations of activity do not support that PAD is solely responsible for this phenomenon (Price, 1972; Price et al., 1971).

Most interneurons in the lower dorsal horn and in the ventral horn also have convergent sensory inputs (Wall, 1967). Early studies showed that both somesthetic and proprioceptive inputs project to intermediate and ventral horn interneurons (Kolmodin, 1957; Kolmodin and Skoglund, 1954). Neurons in this region of the spinal cord respond to interlimb propriospinal inputs (Kolmodin and Skoglund, 1954). Interneurons in the medial intermediate region of the spinal cord (see Kolmodin and Skoglund, 1960) generally respond to afferents from more than one synergistic muscle (Kolmodin, 1957). Many of these interneurons responded to ipsilateral and contralateral proprioceptive inputs, as well as natural stimulation of cutaneous afferents in the ipsilateral toe pad. These results are consistent with anatomical studies which show commissural projections to the contralateral cord from interneurons in the intermediate zone (laminae 5-7) (Mannen, 1975; Matsushita, 1970).

Interneurons situated more ventrally in the spinal cord respond to direct afferent inputs from muscular and cutaneous afferents (Lloyd, 1943a; 1946), other interneurons of the dorsal horn (Wall, 1967; Price et al., 1971), or from descending inputs from the pyramidal (Fetz, 1968; Lund et al., 1965; Lundberg and Voorhoeve, 1962; Lundberg et al., 1963), reticulospinal (Engberg et al., 1968a; 1968b), and vestibulospinal tracts (Erulkar et al., 1966; Wilson and Peterson, 1978). Like the more ventral laminae of the dorsal horn (Price and Mayer, 1974; Wall, 1967), the ventral horn interneurons also exhibit larger receptive fields (Kolmodin, 1957; Price and Mayer, 1974).

Brainstem Inputs Affecting the Excitability of Spinal Reflexes.

Classical studies indicated that structures in the brainstem altered the excitability of spinal reflexes (Sherrington and Sowton, 1915; Matthes and Ruch, 1933; Creed et al., 1932). These early reports did not examine the specific inputs from the brainstem responsible for the changes in excitability of spinal reflexes, although comparisons between spinal reflexes evoked in spinal and decerebrate animals showed that both the FR and CER were inhibited in decerebrate preparations (Sherrington and Sowton, 1915; Matthes and Ruch, 1933). This inhibition was attenuated by transection of the spinal cord or by lesions of the dorsolateral and/or ventrolateral fasciculi of the spinal cord (Fulton et al., 1930a; 1930b; Liddell et al., 1932a; 1932b). Lesions affecting vestibular inputs to the spinal cord failed to diminish the inhibition of the FR in decerebrate preparations (Liddell et al., 1932a; 1932b). Stretch reflexes evoked in extensor muscles, however, were diminished on the same side as the lesion.

The brainstem in decerebrate animals may affect the excitability of spinal reflexes via two principal systems. First, inputs from the vestibular apparatus are conveyed to the spinal cord by the medial and lateral vestibulospinal tracts (MVST or LVST) (Wilson and Peterson, 1981). The other primary descending system from the brain stem is the reticulospinal system which may include indirect vestibular inputs through bilateral connections of the vestibular nuclei with the reticular formation (Gernandt et al., 1959). Medial and lateral reticulospinal tracts originate from the relatively diffuse nuclei of the reticular formation (Peterson, 1979). Since vestibular inputs project bilaterally to the reticular formation, changes in spinal reflexes evoked by reticular or vestibular inputs are often difficult to distinguish (Gernandt et al., 1959; Gernandt and Gilman, 1959).

Early studies showed that vestibular inputs tonically conferred an increase in the excitability of spinal reflexes involving extensor muscles. Unilateral labyrinthectomy or ablation of the vestibular nuclei does result in a loss of ipsilateral extensor tone. This diminished extensor tone is only seen in acute preparations; chronic animals with unilateral lesions exhibit a return of extensor tone. Even bilateral lesions of the vestibular nuclei only produce temporary deficits in the extensor tone which are not accompanied by a reciprocal increase in the excitability of flexor reflexes (Liddell et al., 1932a). Such results illustrate two features of vestibular control of excitability of spinal reflexes. First, the vestibular system contributes strongly to postural reflexes in extensor muscles, although there is also some compensation for the long term loss of vestibular inputs on spinal reflexes. Second, the tonic inhibition of the FR does not originate directly from the vestibular inputs. This non-reciprocal control of flexor and extensor reflexes was considered contradictory to the reciprocal patterns of motor control described by Sherrington (1906a).

Further studies by Gernandt and colleagues also showed that vestibulospinal inputs facilitated extensor reflexes evoked by dorsal root stimulation on the ipsilateral side of the spinal cord (Gernandt et al., 1959; Gernandt and Thulin, 1953; Gernandt and Gilman, 1959). Ventral root reflexes evoked by doral root stimulation concurrent with stimulation of the lateral vestibular nucleus were facilitated through short and long latency paths (Gernandt and Gilman, 1959; Gernandt et al., 1959). The longer latency facilitation was attributed to bilateral projections from the vestibular nuclei to the reticular formation or high cervical spinal cord, since this response could be evoked in the contralateral ventral roots. Intracellular recording techniques later revealed facilitation of excitatory postsynaptic potentials in extensor motorneurones evoked by stimulation of the lateral vestibulospinal tract (Wilson and Yoshida, 1969). The latencies of facilitation indicated that both polysynaptic and monosynaptic paths were involved. Wilson and Yoshida (1969) also noted that polysynaptic EPSPs were more commonly evoked in knee extensors. Monosynaptic excitation of motorneurones by LVST stimulation is directed to motorneurones supplying axial extensor muscles (Precht, 1975). Reciprocal inhibition of ipsilateral motorneurones supplying flexor muscles involved two or more synapses (disynaptic). These results all support a dominant excitatory projection by the lateral vestibulospinal system to ipsilateral extensor motorneurones.

Several features of the anatomical projection of vestibular inputs to the spinal cord are related to vestibulospinal reflexes. Although both the medial and lateral vestibulospinal tracts (LVST) project ipsilaterally to the cervical spinal cord, only LVST axons have been found in the lumbar spinal cord (Wilson and Peterson, 1978). Axons from single neurons in the lateral vestibular nucleus may send collaterals to both cervical and lumbar enlargenments (Abzug et al., 1974). The LVST originates principally from the lateral vestibular nucleus and projects to the ipsilateral spinal cord. Inputs to the lateral vestibular nucleus come primarily from utricular afferents which respond to static position of the head (Peterson, 1970). These results indicate that the lateral vestibular projections to the lumbar cord convey information related to static postural reflexes to both the cervical and lumbar spinal cord.

The pattern of projection of vestibulospinal fibers within the ventral horn of the spinal cord suggests that vestibulospinal reflexes may be subject to modulation by other converging inputs. Vestibulospinal fibers terminate on interneurons in laminae 7-9 in the ventral horn of the spinal cord (Nyberg-Hansen and Mascitti, 1964). Since interneurons in this region of the spinal cord respond to converging inputs from propriospinal and cutaneous inputs (Kolmodin, 1957), vestibular inputs to the lumbar spinal cord of the cat may be modulated by inputs from other sources. A more recent study has indicated that some interneurons responding to vestibular stimulation were also excited by inputs from segmental primary afferents originating in the contralateral limb (Bruggencate and Lundberg, 1974). Erulkar et al. (1966) indicated that vestibulospinal inputs to the spinal cord were responsible for PAD in interneurons, as well as directly affecting interneurons and motorneurons in the lumbar cord of the cat.

Responses evoked by vestibular stimulation are often difficult to reconcile with behavioural responses attributed to the vestibulospinal reflexes. Responses in extensor muscles of the forelimb evoked by sinusoidal (dynamic) linear accelerations of the head (Anderson et al., 1977) are the opposite of the responses evoked by static tilt (Lindsay et al., 1976). Static tilt to one side elicits extension in the limbs of the side tilted down concurrent with head rotation away from the extended limbs, while the limbs on the upward side are flexed (Precht, 1975; Wilson and Peterson, 1978). Dorsoflexion of the head evokes bilateral forelimb extension and hindlimb flexion concomittant with upward rotation of the eyes. The opposite response is evoked by ventroflexion of the head. Quick movements evoking otolith responses result in transient extension of all limbs (Anderson et al, 1977). This response has been related to bracing movement in anticipation of landing after an unexpected fall (Watts, 1976). This response is lost after connections between neck afferents and the reticular formation are severed (Precht, 1975). These results all indicate that higher order interneurons are involved in the integration or expression of vestibulospinal reflexes. Vestibulospinal reflexes may be integratively related to reflexes affected by the reticular formation (including the tonic neck reflexes) (Wilson and Peterson, 1981).

The existence of reticular projections affecting the excitability of spinal reflexes was first suggested by Fulton (1926). Early studies showed that the flexor reflex and CER were tonically inhibited in decerebrate animals (Sherrington and Sowton, 1915; Matthes and Ruch, 1933). Liddell and colleagues (Fulton et al., 1930a; 1930b; Liddell et al., 1932a: 1932b) established that tonic effects from the brainstem remained after lesions of vestibular nerve and ablation of the vestibular nuclei. Lesions of the ventrolateral fasciculi of the spinal cord which severed the vestibulospinal tracts failed to completely suppress the inhibition of the flexor reflex. Only complete transection of the spinal cord or lesions of the dorsolateral fasciculus attenuated the brainstem inhibition of the flexor reflex (Liddell et al., 1932a; 1932b).

Later studies characterized general facilitory and inhibitory regions in the brainstem reticular formation (Magoun, 1950). Stimulation of the lateral regions evoked facilitation of spinal reflexes, while stimulation in more medial regions resulted in inhibition of spinal reflexes. A subsequent study showed that generalized effects on spinal reflexes were only evoked with high intensities of stimulation (Sprague and Chambers, 1954). Low levels of stimulation evoked coordinated movements of the whole animal. These studies indicated that certain regions of the reticular formation were responsible for general changes in reflex excitability, while supporting a complex integrative function for the reticular formation in reflex organization.

The predominant projection from the reticular formation to the lumbosacral spinal cord originates from nuclei located in the medial brainstem (Peterson, 1979). The medial reticulospinal tract, located in the ventromedial fasciculus of the spinal cord projects to all levels of the spinal cord, although most terminals are located rostral to the first lumbar segment of the spinal cord. The lateral reticulospinal tracts, ipsilateral and contralateral, terminate in more dorsal laminae at all levels of the spinal cord (Nyberg-Hansen, 1965). Single lateral reticulospinal fibers terminate in both cervical and lumbar segments of the spinal cord (Peterson et al., 1975). The anatomical projection of these ventrally located reticulospinal tracts indicates a capacity to effect reflex activity at both cervical and lumbar levels of the spinal cord as well as functional distribution to many laminae of the spinal cord.

In contrast to the vestibulospinal system stimulation of the reticulospinal system evokes direct action on both flexor and extensor motorneurons (Grillner and Lund, 1968). Stimulation of the MRST evokes primarily monosynaptic EPSPs or IPSPs in motorneurons supplying the axial musculature. LRST stimulation evokes polysynaptic responses in motorneurons supplying more distal muscles (Wilson and Yoshida, 1969). Although it is often difficult to relate isolated responses in motorneurons or interneurons to the expression of complete behavioural responses, activity in the ventral reticulospinal tracts has been related to short and long spinal propriospinal systems in the spinal cord (Wilson and Peterson, 1981). The early studies of Lloyd (1941) characterized a long bulbospinal system which involved activation of segmental and intersegmental propriospinal neurons. Later studies showed that both short and long descending propriospinal systems were related to reticular inputs from the brainstem in decerebrate cats (Gernandt and Shimamura, 1961; Shimamura and Livingston, 1963). These results, considered together, suggest a complex interaction between ascending propriospinal and descending propriospinal systems mediated by relays in the reticular formation (Wilson and Peterson, 1981).

A putative reticulospinal pathway in the dorsolateral fasciculus has been physiologically characterized, but has resisted anatomical analysis. These more dorsally located reticulospinal tracts include the descending raphe system (Basbaum et al., 1978) and the dorsal reticulospinal system described by Lundberg and collaberators (Eccles and Lundberg, 1959; Holmqvist and Lundberg, 1961). Although these tracts originate from different regions of the medial brainstem, they travel in anatomically similar locations and project to anatomically similar areas in the dorsal and ventral horns of the spinal cord (Brown, 1981). The terminations of these tracts are located in laminae 1,2,5,6, and 7 of Rexed (Basbaum et al., 1978). Such anatomical connections suggest a function in the control of afferent input as well as reflex activity.

Activity in the dorsal reticulospinal system in the decerebrate animal has been associated with the tonic inhibition of polysynaptic flexor and crossed extensor reflexes (Eccles and Lundberg, 1959; Holmqvist and Lundberg, 1961). Reflexes evoked in ventral roots by stimulation of large afferent nerves (Ia) are spared from decerebrate inhibtion. In fact stimulation of Ia afferents in decerebrate preparations presynaptically inhibits the transmission evoked by concurrent stimulation of FRAs (Anden et al., 1966a). Transection of the spinal cord attenuates the tonic inhibition of polysynaptic FRs and CERs (Eccles and Lundberg, 1959). Stimulation of FRAs in spinal animals evokes a presynaptic inhibition (PAD) in the terminals of Ia afferents (Lund et al., 1965). These effects are further facilitated by concurrent administration of DOPA to acute spinal preparations (Anden et al., 1966a; 1966b; Jankowska et al., 1967a; 1967b). Further studies indicate that the release of polysynaptic reflexes from tonic inhibition by such methods is associated with spontaneous locomotor responses (Grillner, 1975). These studies indicate that the polysynaptic reflexes of flexion and crossed extension may be integratively related to locomotion as well as nocifensive behavior.

Although it is known that DOPA facilitates polysynaptic reflexes in the spinal cord, little is known of the mechanism by which this activity is mediated (Willis, 1982). Part of the problem stems from the multitude of different reticular paths to the spinal cord. These paths may release a variety of neurotransmitters. Some early studies indicated that the effect of DOPA was related to liberation of norepinepherine or other monoamine neurotransmitters in the spinal cord, however depletion of norepinepherine terminals by administration of reserpine does not result in depression of the enhanced polysynaptic reflexes by subsequent administration of DOPA (Engberg et al., 1968c). It is likely that more than one neurotransmitter is involved in the augmented discharge in polysynaptic reflexes associated with the effects of DOPA (Krnjevic, 1981).

The tonic neck reflexes evoked from spindle receptors in the large muscles of the neck (Abrahams, 1977) and joint receptors in the high cervical vertebrae (McCouch et al., 1951) by rotation of the neck or head are mediated through the reticular formation (Wilson and Peterson, 1981). Lindsay et al (1976) distinguished between labyrinthine and tonic neck reflexes by casting the neck of decerebrate cats which allowed examination of labyrinthine effects or by fixing the head and rotating the body around the head. The latter manipulation eliminated vestibular contributions to the reflexes evoked. Rotation of the body evoked extension in the limbs towards which the chin of the animal was pointed. The limbs on the occiput side of the head were flexed. These results supported classical studies by Magnus (1926) who utilized labyrinthectomized animals to isolate similar tonic neck responses. A complex interaction of inputs from the labyrinths and receptors in the neck results in the static righting reflexes observed in decerebrate animals.

METHODS AND MATERIALS

Surgical Techniques

Eleven cats of mixed breeds (1.0-2.1 kg.) were first anesthetized with ethyl ether. The trachea was cannulated with a stainless steel tube in order to prevent reflux of oral contents and to provide access to a ventilation pump which was only used in a few instances when the animal failed to respire during the procedures. In most cases the pump was never required. The common carotid arteries were ligated in the neck to minimize circulation to the upper brain.

The animal was rotated into a prone position for decerebration and subsequent surgical procedures. A trephine and rongeur were used to remove enough cranial bone to expose the cortex, then the neuraxis was transected at the midcollicular level with a blunt spatula, using the bony tentorium as a guide. Bleeding was minimized during the actual decerebration procedure by manual compression of the vertebral arteries against the atlas vertebra. Following transection of the neuraxis, the arterial compression to the vertebrals was applied intermittently, as required to allow perfusion of brainstem structures with minimal bleeding. After several minutes, sufficient clotting occurred to permit uninterrupted perfusion through the vertebral arteries. A ligature placed through the scalp was used to suspend the head in a slightly ventriflexed position so that any transudated fluid or blood drained to the nasal end of the evacuated cranial cavity rather than along the brainstem.

The sciatic nerve in each of the hindlimbs was exposed in the popliteal fossa and was followed superiorly by dissection along the femur, where it was ligated near the mid point of the femur and cut distal to the ligatures. Branches of the sciatic supplying the hamstring and gluteal muscles in the right leg were cut to prevent coactivation of flexors and hip extensors during stimulation procedures. The right femoral nerve was exposed with the animal in an approximately supine position and all branches were sectioned except those supplying the quadriceps femoris. Identification of the branches to the quadriceps was accomplished by visualizing contractions of these muscles evoked by electrical stimulation of the different nerve branches. Two indwelling electrodes were inserted into each of the severed sciatic nerves just proximal to the ligatures. The .127 mm diameter wire electrodes were fully insulated except for the tips, which were scraped to make good electrical contact. Short pieces of latex surgical tubing were used to enclose the electrode-nerve complex to provide insulation from surrounding tissues.

The cat was then placed in the supine position and the quadriceps muscle and patellar tendon were resected and dissected free from the surrounding tissues. Heavy surgical suture was used to fasten the patellar tendon to an isometric muscle tension transducer. The entire right hindlimb was stabilized vertical to the table by drill bits inserted in the femur at the distal (knee) and proximal (hip) ends of the bone and clamped to a vertical supporting rod. All structures of the right hindlimb were oriented vertical to the table.

Stimulation/Recording Techniques

The sciatic nerves were stimulated with square wave pulses administered through stimulus isolation units. Stimulus frequency, intensity, and duration for each electrode pair could be adjusted independently. Stimulus parameters were adjusted to produce a brisk response from the quadriceps muscle; the levels were varied for different experimental procedures.

Crossed extension reflexes were monitored by recording isometric tension from the right quadriceps muscle on an ink-writing curvilinear oscillograph. The gain of the amplified signal was adjusted to provide a reasonable visual trace of the evoked response. Paper speed was varied to facilitate evaluation of different types of responses to the experimental procedures. Calibrations were obtained at each setting by suspending a standard unit of weight from the muscle tension transducer.

Experimental Protocol

In early experiments the threshold intensity sufficient to evoke the CER was determined at relatively high frequencies of stimulation (>10 herz). The range of threshold intensities was between 0.05 ma. and 5.0 ma. With the subsequent observation that CERs could be evoked by single shocks when animals were on their right side, thresholds were determined with low and high frequency stimulation. The intensities required to evoke the CER with single stimuli were between 0.25 and 0.5 ma.

Examinations of reflex summation were performed with suprathreshold intensities of stimulation (0.5-2.5 ma.) at various frequencies. A typical experimental series consisted of examining responses evoked using slow trains of stimuli at intervals between 7 seconds and 0.1 seconds. Then a conditioning-test paradigm was used. The effects of a conditioning stimulus (C) on the response to a test shock (T) were examined at different C-T intervals.

Inhibition of the CER in response to stimulating the right sciatic nerve was accomplished by using low frequency trains of stimulation. Prolonged CERs were first evoked by iterative stimulation of the left sciatic nerve (10 hz). After the reflex tension had plateaued, stimulation of the right sciatic ensued. Trains of inhibitory stimuli were delivered to the sciatic at frequencies between 0.3 hz and 20 hz.

RESULTS

General Considerations

All the decerebrate animals exhibited the classic signs of tonic extensor rigidity (Sherrington 1898). Rigid extensor tone was observed in all limbs within minutes of the surgical decerebration. Forelimb extensors resisted stretch until adequate force induced the "clasp knife" effect (Sherrington 1906). In a few preparations the rigidity was profound enough to cause axial muscle rigidity in the neck (opisthotonus). Static righting reflexes were also present in the decerebrate cats (Magnus 1926). The extensor tone was more pronounced on the side of the animal in contact with the table.

Several postural reflexes in these acute decerebrate cats were visually observed but not directly recorded on to the oscillograph. Movement of the head to the left or right consistently evoked a rotation of the body to the side in which the head was turned. Postural movements in the forelimbs also were produced by rotating the animal from side to side. Rotation of the cat from right to left evoked a reflex flexion of the left forelimb and extension of the right hind limb. Although the left forelimb would return to an extended posture, the limb could be forcibly flexed with minimal effort. The right forelimb (in contact with the table surface) remained very rigid. Passive flexion of the limb could only be accomplished with considerable force. These observations are consistent with reflex movements attributed to postural mechanisms and static righting reflexes (Magnus 1926).

Several animals developed clonic contractions in the muscles of the fore- and hindlimbs when the sciatic nerves were stimulated. The frequency of the beats of clonus ranged between 1.5-3.5 herz; this frequency was not related to the frequency of stimulation of the sciatic nerves. Preparations showing a high degree of spontaneous activity seemed more predisposed to developing clonic activity. The clonus often persisted even after prolonged bouts of high intensity and high frequency stimulation.

Influences of Different Sensory Inputs on CER Excitability

Effects of Body Position. In the first two experiments, cats were placed with their left lateral body surface on the table surface with the right hindlimb supported as described in the methods. The CER in these preparations could only be generated by high frequencies of stimulation (>10 herz) (cf. 1). Rotation of the animal so that the right side was on the surface resulted in brisk CERs evoked by single stimuli. Single brief stimuli (1ms) elicited brisk CER "twitches" from the right quadriceps muscle. The same stimuli evoked no demonstrable reflex while the cat was positioned upon the left lateral surface (cf. 1 and 2). Changing the body position also affected the excitability of a sustained CER evoked by high frequency stimulation (10 herz) (cf. 1 and 3). During low frequency stimulation, rotation of the body from left to right evoked different responses (cf.2). First, CERs evoked by single shocks were only seen when the cat was

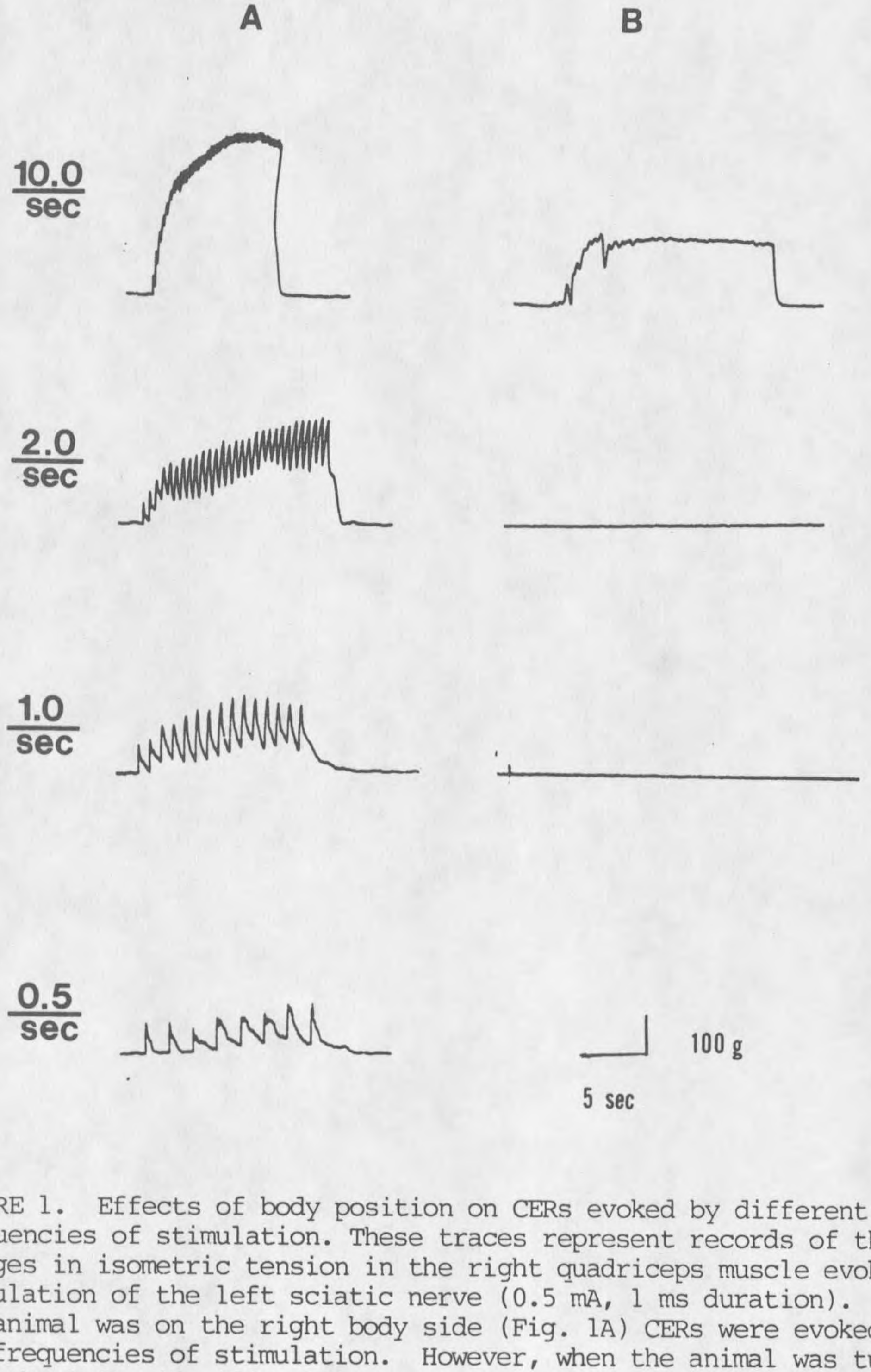

FIGURE 1. Effects of body position on CERs evoked by different frequencies of stimulation. These traces represent records of the changes in isometric tension in the right quadriceps muscle evoked by stimulation of the left sciatic nerve (0.5 mA, 1 ms duration). When the animal was on the right body side (Fig. 1A) CERs were evoked at all frequencies of stimulation. However, when the animal was turned onto the left side (Fig. 1B) CERs were only evoked by a frequency of 10 hz.

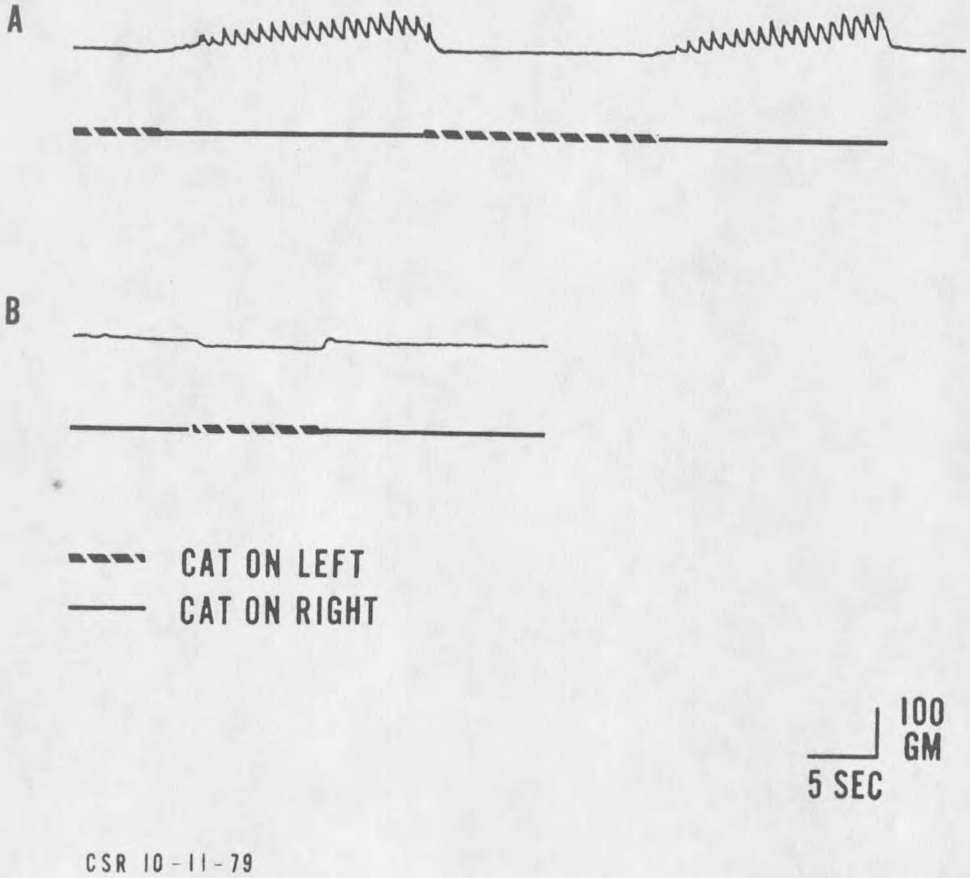

FIGURE 2. Effects of body rotation on CERs evoked by low frequency stimulation. In this preparation the animal was rotated from the left side to the right side twice. The left sciatic was stimulated at a constant frequency of 1 hz (0.5 ma). CERs were evoked only when the animal lay on the right side (A). No significant change in isometric tension was recorded in the absence of stimulation (B), showing that changes in the CER evoked by body position are direct rather than secondary to some other factors.

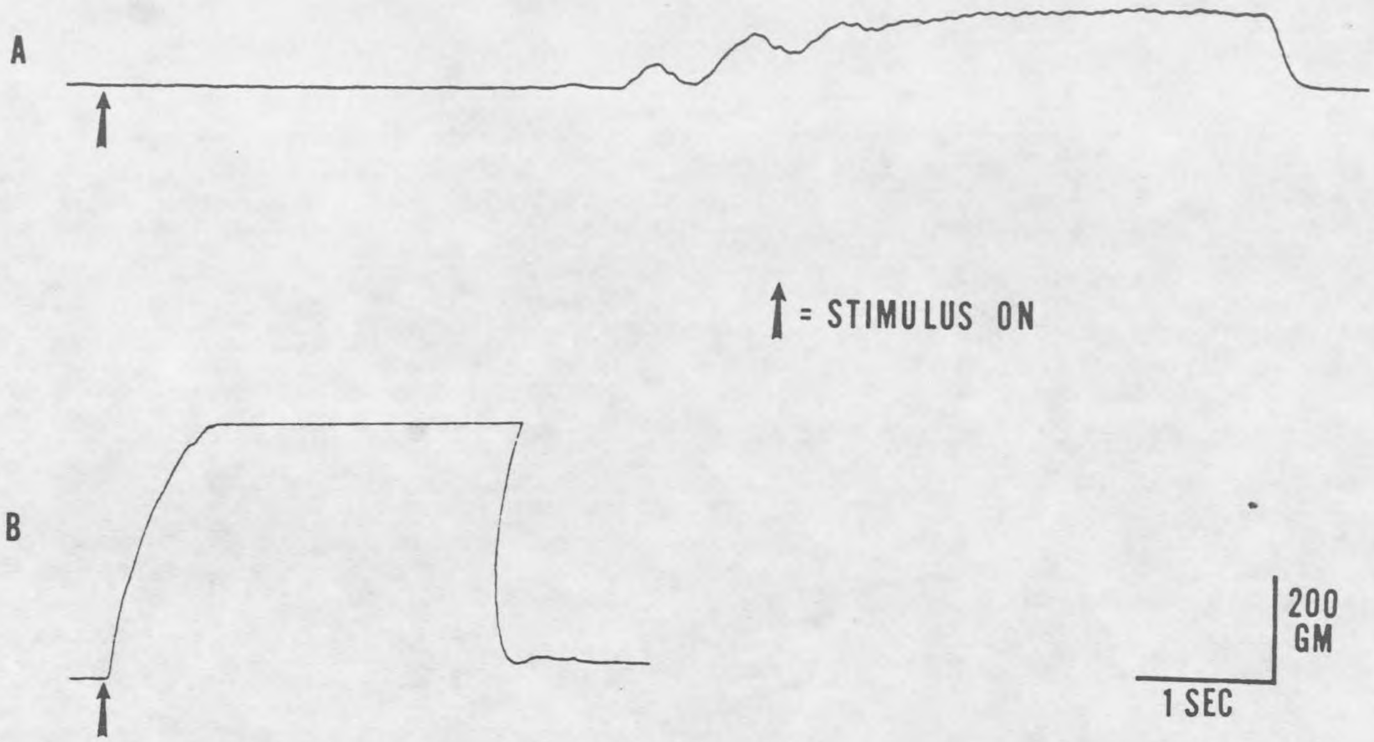

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FIGURE 3. Effects of body position on the latency of the CER response. In this experiment the sciatic nerve was stimulated at a frequency of 10 hz. Arrows denote the application of stimulation. In the top trace the animal lay on the left side. The lower trace indicates the response with the animal on the right surface. The sensitivity of the recording of isometric tension was higher than usual to illustrate differences in the latency of the CER. With the cat on the right the response was much quicker (<50ms) and more vigorous, than when the cat was placed on the left side.

placed on the right side of the body. The lower trace of Fig. 2 illustrates that the tension recorded when the body position was changed was not directly due to a postural reflex response, but was a true CER evoked by nerve stimulation. The magnitude of the CER response varied with body position. The peak tension evoked with the preparation on the right lateral surface always exceeded the tension produced with the animal on the left lateral surface (cfs. 1 and 3).

The latency of the CER response evoked by high frequency stimulation varied greatly with different body positions (cf. 3). Placement of the cat on its right body side consistently yielded a short latency (<50ms) response. Similar parameters of stimulation evoked a weak and delayed response when the cat was on its left body side. In some preparations the latency of the reflex response exceeded 2 to 3 seconds when the animal was on the left body surface.

The changes in excitability of the CER response related to body position were the most consistent observations of the study. All preparations exhibited a pronounced change in the excitability of the CER with changing body position. The consistent change may be related to the quantity and variety of inputs, including proprioceptive, mechanoreceptive, and vestibular, induced by rotation of the entire body.

Effects of Head Rotation. When examining effects of head rotation, a sustained CER was evoked by iterative high frequency stimulation with the cat in a supine position. When the response reached a steady level, the head was rotated to one side or another. Rotation of the head to the right facilitated the CER recorded from

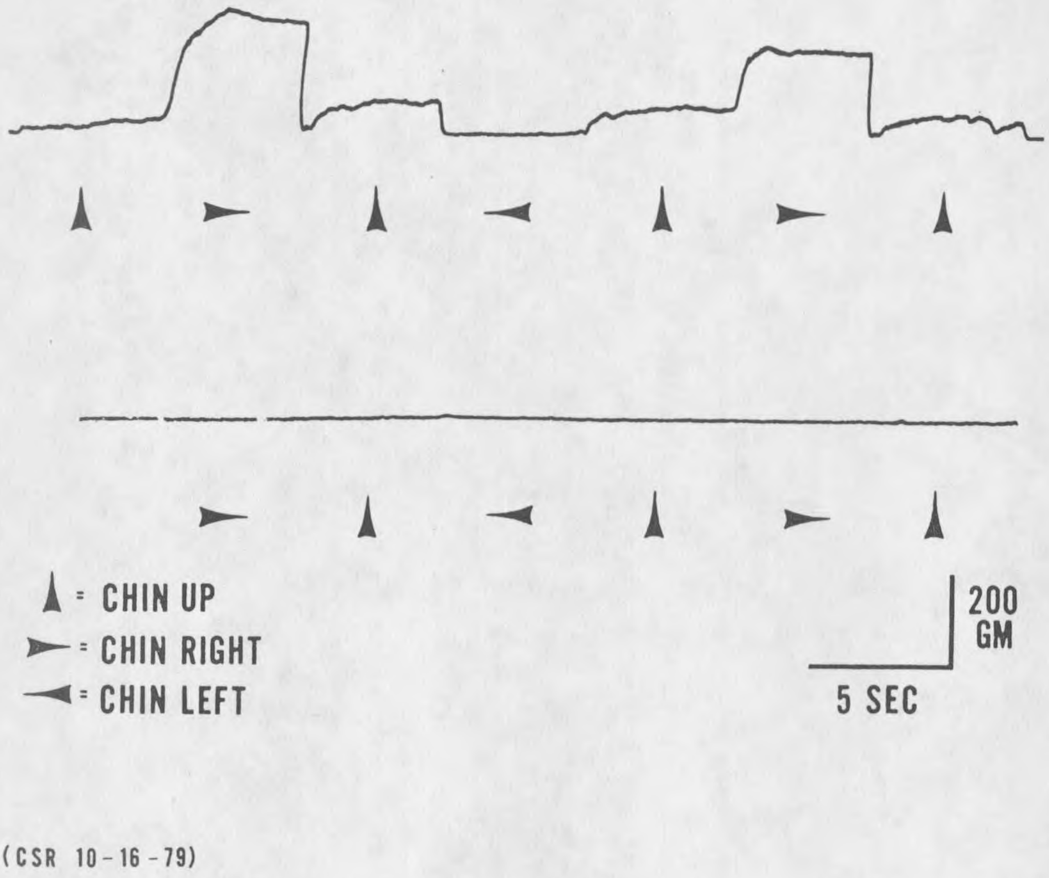

FIGURE 4. Effects of rotation of the head on the CER. A prolonged CER was first evoked by repetitive stimulation (10 herz, 0.5ma). The reflex was then facilitated or inhibited by rotation of the head to the right or left respectively. Position of the head in the horizontal plane produced an intermediate CER (top trace). No responses were evoked by rotation in the absence of stimulation (bottom trace).

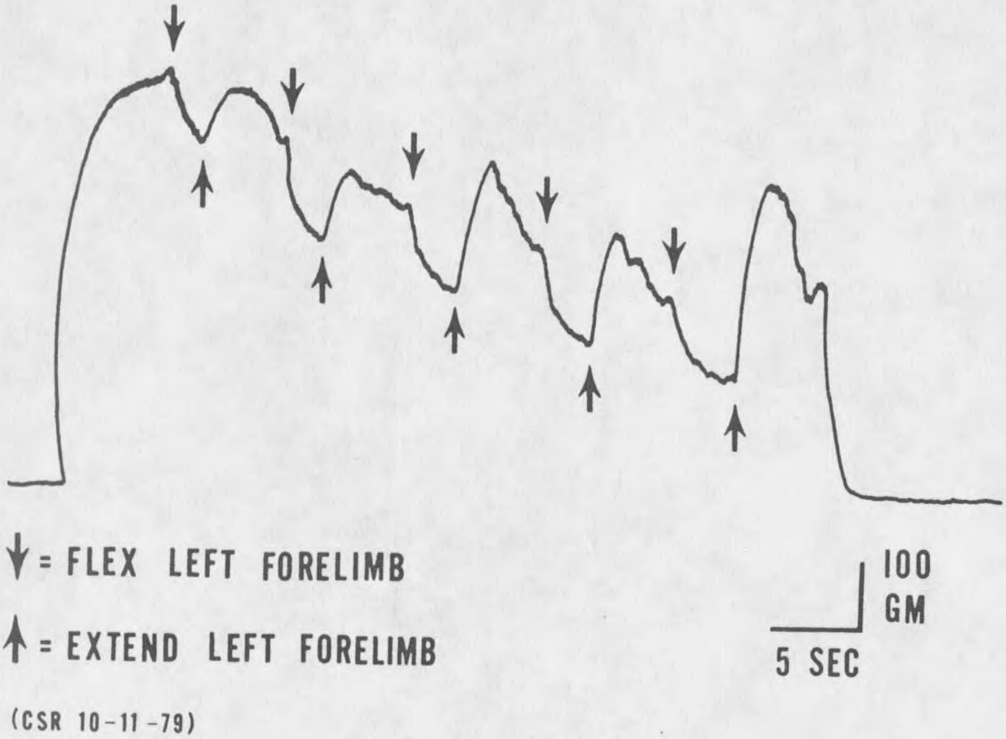

FIGURE 5. Effects of passive flexion of the left forelimb on CERs evoked by repetitive stimulation. In this preparation repeated flexion inhibited the CER evoked by iterative stimulation (10 herz). Arrows pointed down indicate the onset of flexion. Upward arrows indicate release of flexion. Release from flexion of the forelimb evoked a facilitation of the CER in this animal.

the right quadriceps. Rotation of the head to the left of midline (supine) depressed the CER (cf. 4). The "neutral" or intermediate position is defined when the animal is supine with the nose pointed vertically. On several occasions the initiation of any movement to the left produced a transient inhibition during the actual rotation of the head. The level of tension in the CER evoked by head rotation was dependent on the final position of the head.

In one preparation the head was held in a vertical position while the body was rotated about the neck and head. A CER response similar to that recorded in Fig. 4 was observed. Facilitation was seen with dextrorotation while rotation to the left inhibited the reflex response. An intermediate tension level was obtained when the animal was in the intermediate position.

Dorsiflexion, ventroflexion, and any lateral flexion of the head elicited a very weak response or no response. Transient inhibition of the CER during the manipulations was observed on occasion. Responses to neck rotation were more limited and not as vigorous as effects seen with rotation of the body.

Effects of Forelimb Manipulation. A sustained CER evoked in the right quadriceps was first generated by iterative stimulation of the left sciatic nerve. The extended left forelimb was flexed at the knee by manual force. The resulting inhibition was most pronounced if the tonic extension created by the decerebrate condition and sciatic stimulation was overcome by the force ("clasped knife effect") (cf. 5). On some occasions there was a facilitory rebound of the CER tension when the flexion of the left forelimb was released. Rebound

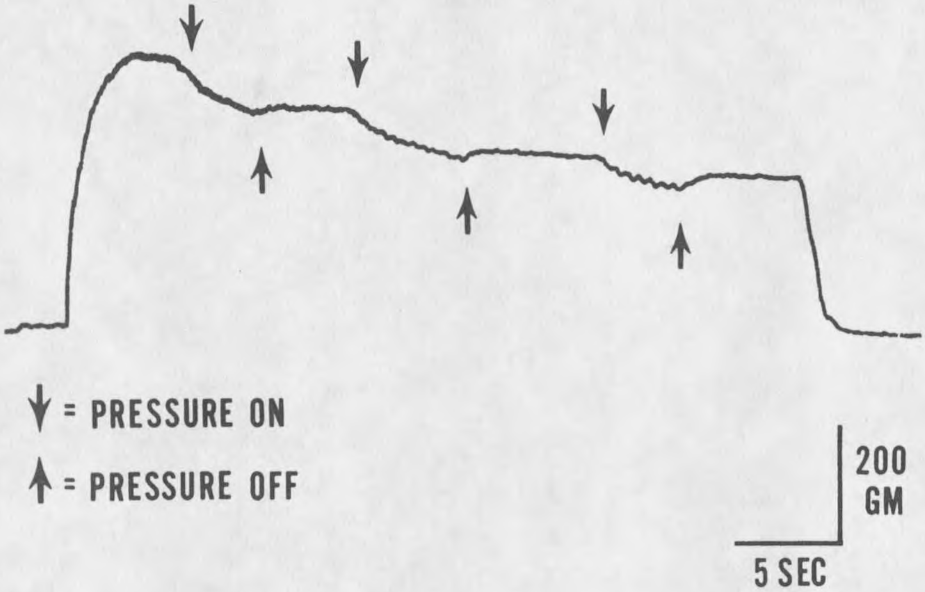

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FIGURE 6. Effects of mechanoreceptor input on CERs evoked by repetitive stimulation. In this experiment a weight approximating the animal´s weight was placed on the left body surface while the cat lay on the right side. Inhibition of the CER is seen during the application of the stimulus (between the arrows).

phenomena in reflex action has been described as an inhibition disguised by the coactivation of more dominant facilitory actions (Creed et al. 1932; Denny-Brown 1928). Flexion of the forelimb evoked reflex postures in the opposing forelimb. The extension of the opposite forelimb is consistent with Sherrington's concept of reciprocal and double reciprocal organization of spinal reflexes (Sherrington 1906a).

Several further manipulations of the forelimbs were performed with inconsistent effects on the CER. Hyperextension of the left forelimb and flexion or extension of the right forelimb elicited weak or no responses.

Effects of Mechanoreception. In six animals a continuous CER was evoked by iterative stimulation when the animal was placed with the right side on the table. At the peak of the tension produced by the CER, pressure was applied to the left lateral surface of the animal, placed either by a hand or a flat board. Attempts were made to have the force applied approximate the weight of the animal. Each time pressure was applied there was a reduction in the CER. The inhibition produced was weak in even the most responsive preparation, but was seen in all instances (cf. 6).

Rebound and Clonus. Rebound contractions were often observed upon the termination of procedures which inhibited the CER. In many instances a post stimulus facilitation of the CER was observed after termination of stimuli subthreshold for evoking an inhibition of the CER. On occasion subthreshold inhibitory inputs would precipitate clonic contractions of the limbs. Clonus in these instances may

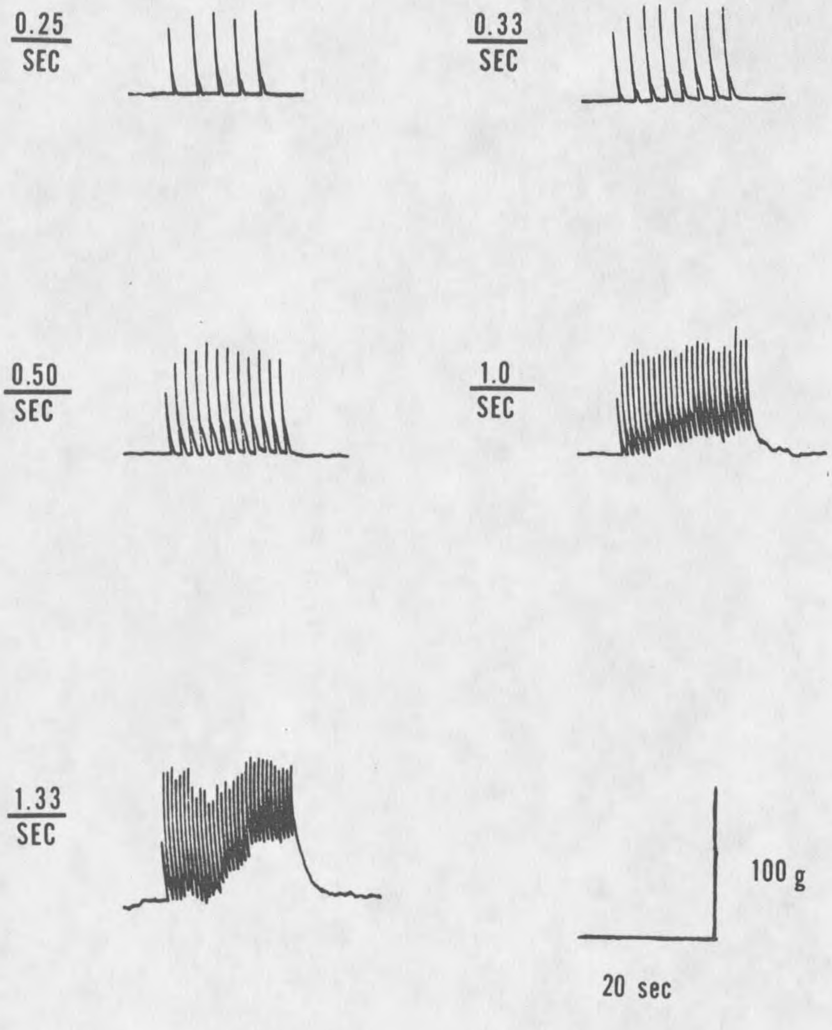

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FIGURE 7. Reflex summation of the CER evoked by single shocks at different frequencies. This animal was placed on its right side. The left sciatic was stimulated at the three frequencies indicated (0.5ma). At a frequency greater than 0.5 herz the CERs began to summate (tension failed to return to original value). A short latency response (spike) was followed by a prolonged response (hump) (indicated by slow return to original tension) with each stimulus and at each frequency.

FIGURE 8. Summation in late CERs evoked by low frequency stimulation. This preparation exhibited increases in the late tension response with very low frequencies of stimulation (0.25 and 0.14 herz). Early responses (short latency spikes) were not significantly different in size at both stimulus frequencies. Delayed responses (immediately following each spike) recruited at both stimulus frequencies.

represent an unbalancing of facilitory and inhibitory inputs which produce a series of sequential episodes of facilitation and inhibition. The rhythymical contractions could represent a partial activation of neurons capable of pattern generation.

Effects of Stimulus Frequency on Reflex Recruitment

Reflex recruitment. Different frequencies of stimulation were used to examine prolonged central summation of the CER. An adequate (suprathreshold) stimulus intensity was used to provoke a consistent reflex response. The threshold intensity for the CER varied between preparations (0.05 ma to 0.25 ma). A stimulus intensity of 0.5 ma was generally used. Increasing the stimulus intensity above 1 ma produced no further change in the reflex response. The animal preprarations were placed on the right lateral body surface to facilitate the CER evoked by single shocks.

The first two animals were not positioned on the right lateral surface. No CERs were evoked by single stimuli in these preparations. CERs were only evoked with higher intensities and frequencies of stimulation.

In subsequent experiments high frequencies of stimulation of the left sciatic (10 herz) evoked a brisk response with the cat on the right lateral surface. The same frequencies of stimulation produced a delayed and more slowly recruited response when animals were placed on the left side (cf. 3).

CERs evoked by successive single stimuli display two principal features which are consistent with prolonged central summation of

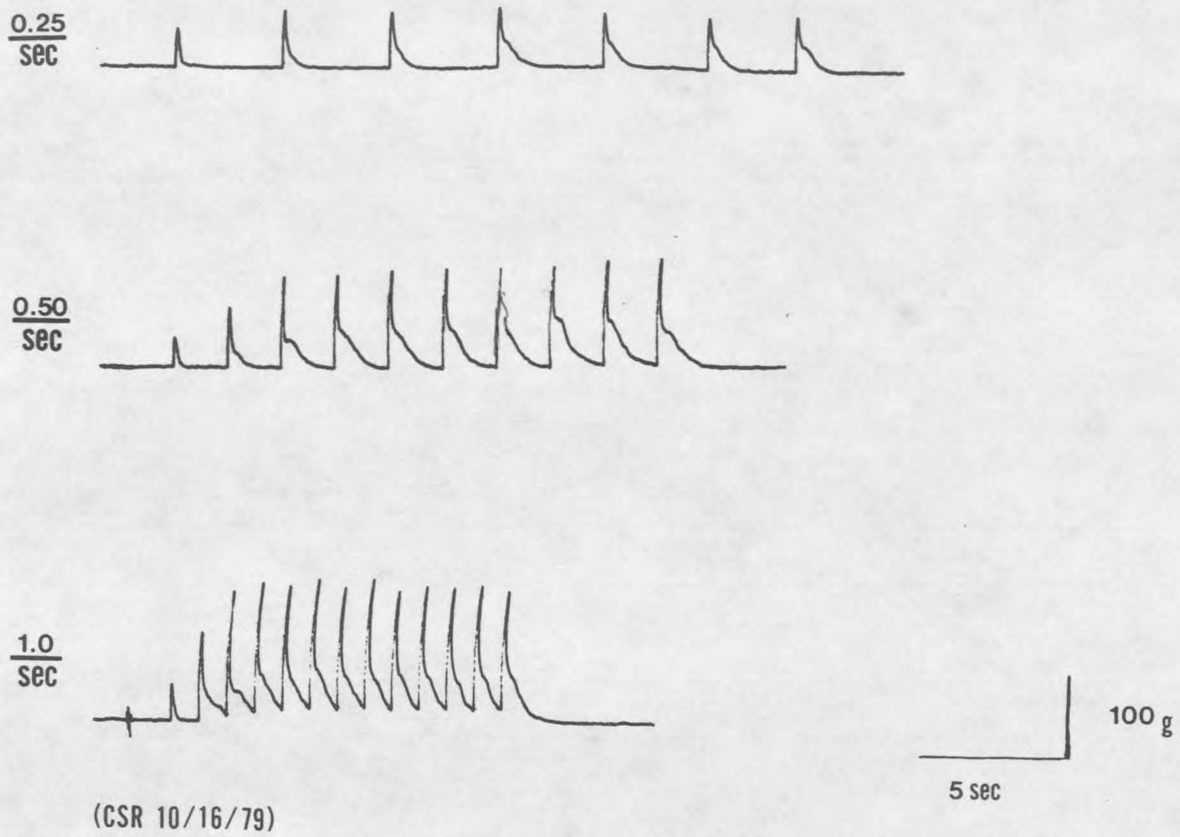

FIGURE 9. Effects of stimulus frequency on recruitment of CER early (spike) and late (hump) responses. In this cat CERs evoked at three different stimulus frequencies (0.25, 0.5, and 1.0 herz) all exhibit developing early and late responses (spike-hump pattern). At frequencies greater than 1.0 herz (0.5 ma) the CER fails to return to the original tension. The prolonged discharge (late response) prevents complete relaxation between succeeding responses.

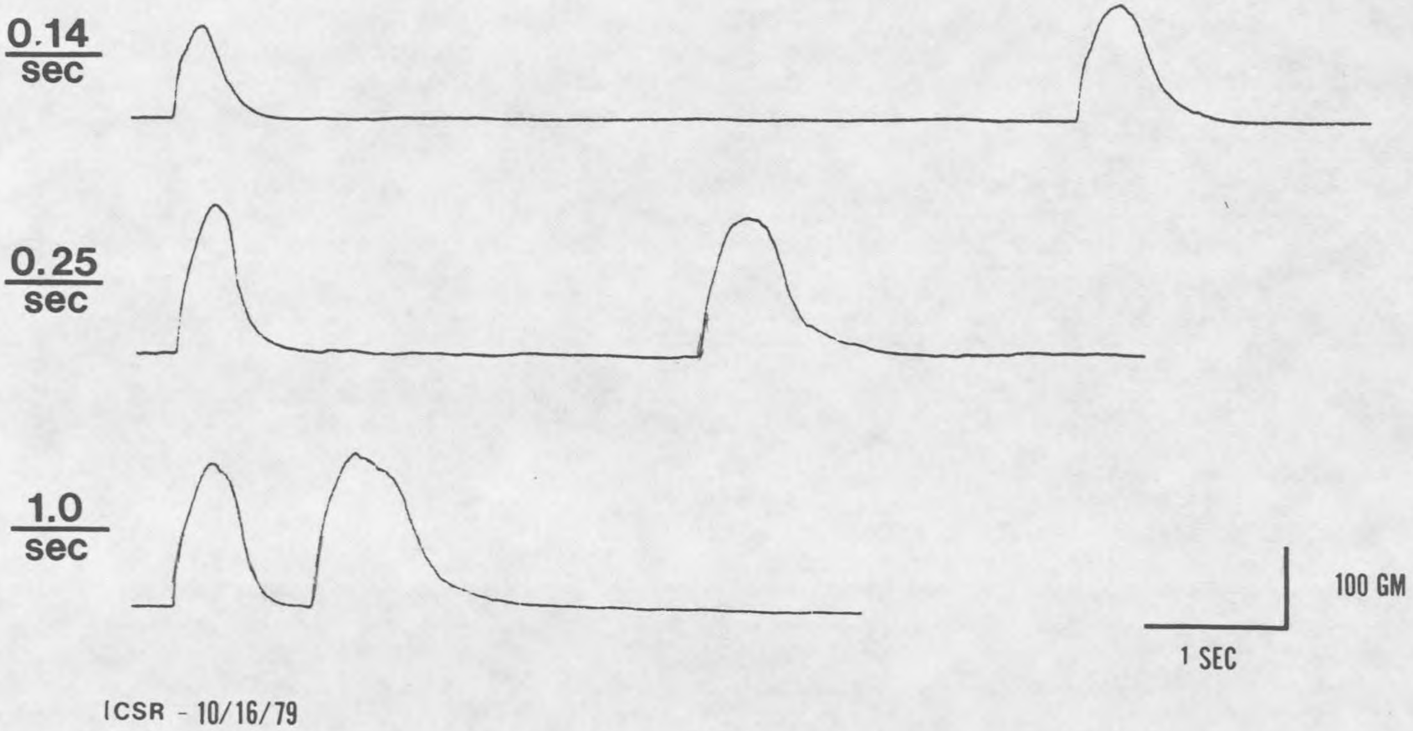

FIGURE 10. Two consecutive CERs responding to single shocks with different frequencies of stimulation (high paper speed). At all three frequencies (0.14, 0.25, and 1.0 herz) this animal showed a stronger second response indicated by a longer duration of the CER. The second response at 0.25 and 1.0 herz appears significantly different than the first responses.

nocifensive reflexes. First, single stimuli evoke a brisk short latency response followed by a protracted longer latency response. The shorter latency response exhibited a rapid rise in muscle tension (cf. 7). This was termed the "spike" in the present investigation. A slower rise and more protracted duration was characteristic of the longer latency CER. This part of the two phase CER was referred to as the "hump" response (cfs. 7,8,9). On several occasions the delayed response (hump) evoked by a single stimulus actually appeared as a completely distinguishable second response (cf. 11). Some CERs evoked by a single stimulus lasted more than one second (cf. 12). The second feature of the summation of CERs evoked by single shocks was the augmented late response with successive stimulation at low frequencies (cfs. 8 and 9). At intervals of stimulation less than 2 seconds the delayed discharge was observed to summate with successive stimuli. The recruited late response outlasted the interval between shocks, so the muscle never completely relaxed during the period of stimulation (cfs. 7-12). The short latency part of the double response of the CER did not exhibit such a pronounced recruitment of the amplitude or duration with such low frequencies of stimulation (cfs. 7,8,9,11).

In one particular experiment the prolonged central summation was examined by giving paired shocks at varying intervals (cfs. 10 and 12). At intervals up to seven seconds (cf. 10) the second response of the pair had an increased duration indicated by a more rounded contour. Such changes were much more evident with intervals of stimulation less than 4 seconds. In one set of experiments paired shocks, 1.5 sec. apart, were given every 4.5 seconds (cf. 12). Each

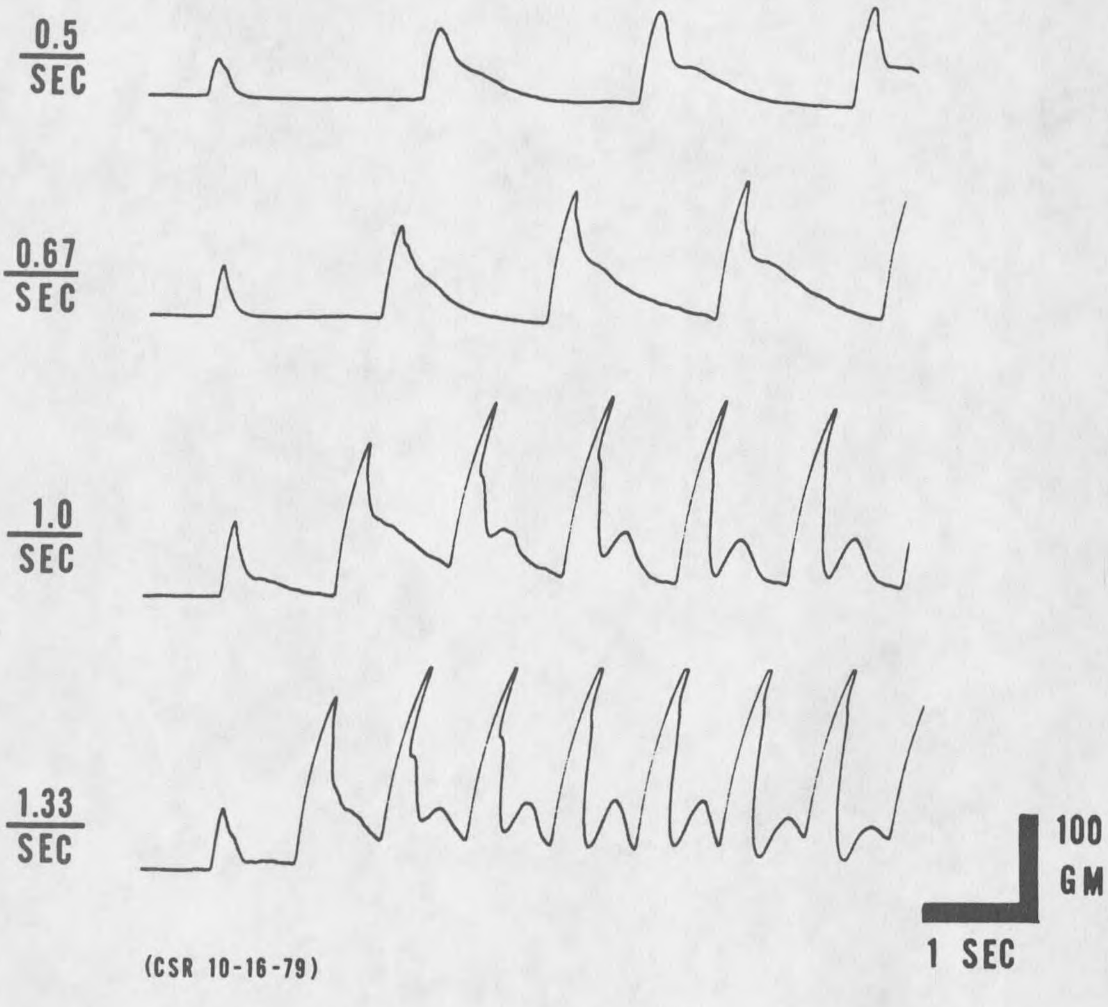

FIGURE 11. Recruitment of delayed CERs (hump) with increases in stimulus frequency. CERs evoked at the slower two frequencies produce smaller and less distinct delayed responses. At higher frequencies (1.0 and 1.33 herz) delayed CERs were seen to form distinct second responses with succeeding single shocks.

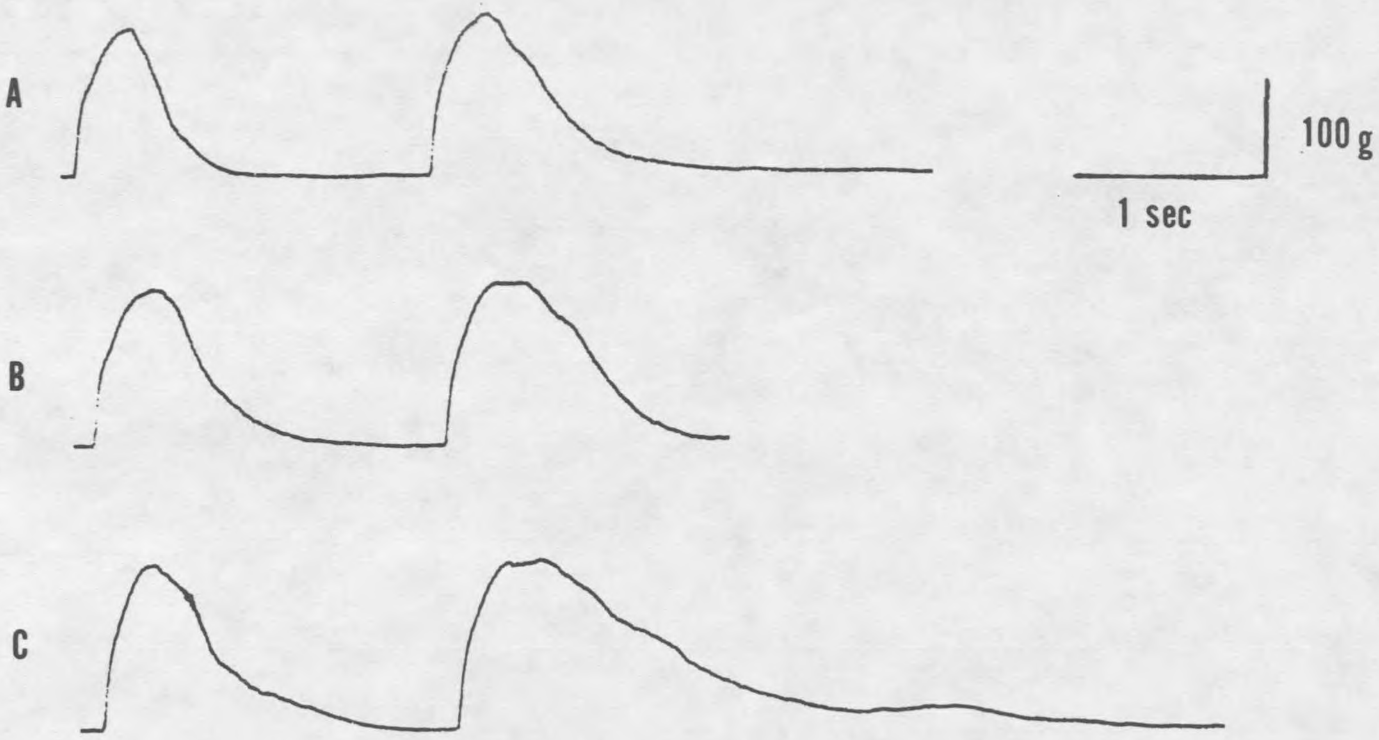

FIGURE 12. CERs evoked by successive pairs of shocks at a 4.5 second interval. In this experiment CERs to single shocks (0.67 herz) were elicited. The interval between the three sequential trials (A,B, and C) was 4.5 seconds. Some increase in duration is indicated between first and second responses in each trace. The second response in the last trace (C) is significantly longer in duration than the second response of the first trace (A).

succeeding pair showed increased durations of activity. The second response of each pair exhibited progressive summation whereas the first response remained fairly constant.

In one particularily hyperreflexic preparation there was a prominent afterdischarge evoked by low frequency stimulation (cf. 8). Intervals of stimulation less than 4 seconds produced lengthened durations of response, although the peak tensions remained similar. Of special interest were the differences in duration and tension of these responses. Summation of the CER required a stimulus interval of about 2.0 seconds (cf. 1A, 9, and 11), yet lower frequencies of stimulation evoked subtle changes in the duration of the reflex responses to single shocks (the later discharge or hump) (cfs. 7, 8, 9, 10, and 12).

Reflex Inhibition. The CER in the right hindlimb was consistently inhibited by stimulation of the right sciatic nerve. As with excitation of the CER (see above) the inhibition evoked by stimulating the ipsilateral nerve was dependent in part on frequency of stimulation. The right sciatic nerve was stimulated with similar intensities of stimulation used to evoke the CER by stimulation of the left sciatic nerve. Stimulation of the right sciatic with low frequencies of stimulation (<1 hz) failed to completely inhibit a CER evoked by iterative stimulation (10 hz) (cf. 14). Stimulation of the right sciatic with higher frequencies (>2 hz) evoked a summation of the inhibition of the CER. Higher frequencies of stimulation (>10 hz) were capable of inhibiting the CER completely.

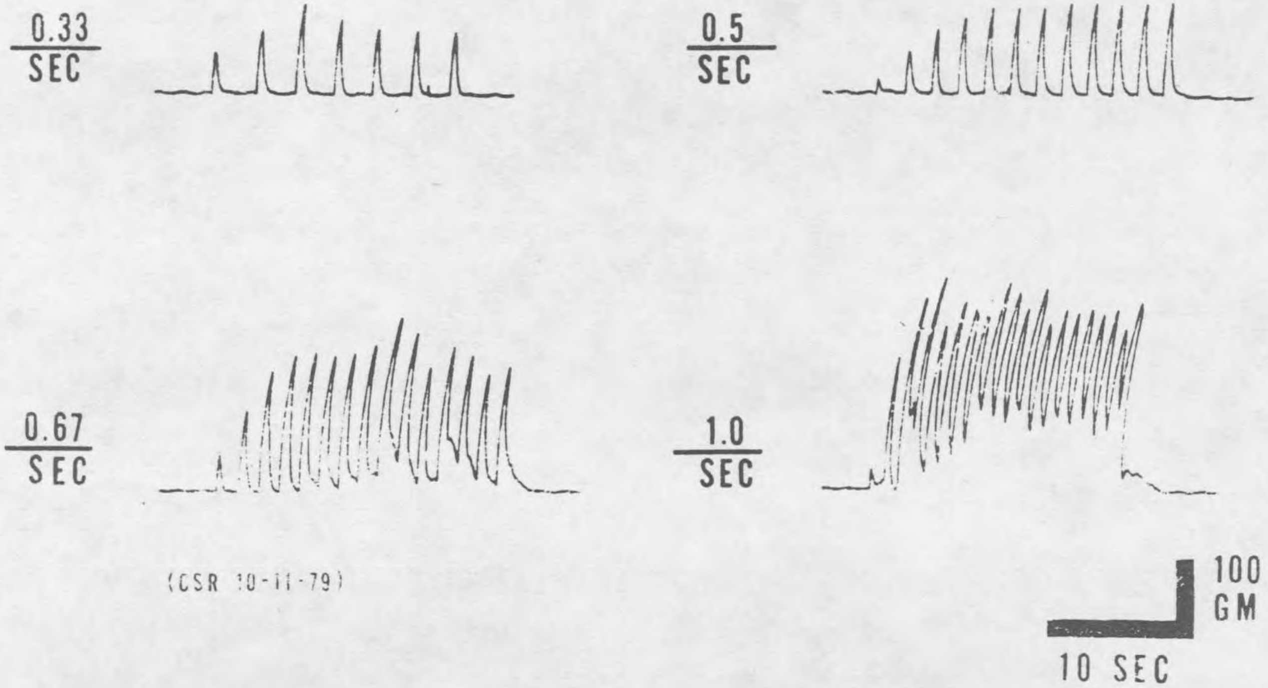

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FIGURE 13. Reflex summation in response to different stimulus frequencies. A different preparation´s responses to different frequencies of stimulation illustrate recruitment of a delayed response with low frequency stimulation (0.67 herz). Although a late response is not as apparent in this experiment spike responses recruit at low frequencies of stimulation (0.5 herz).

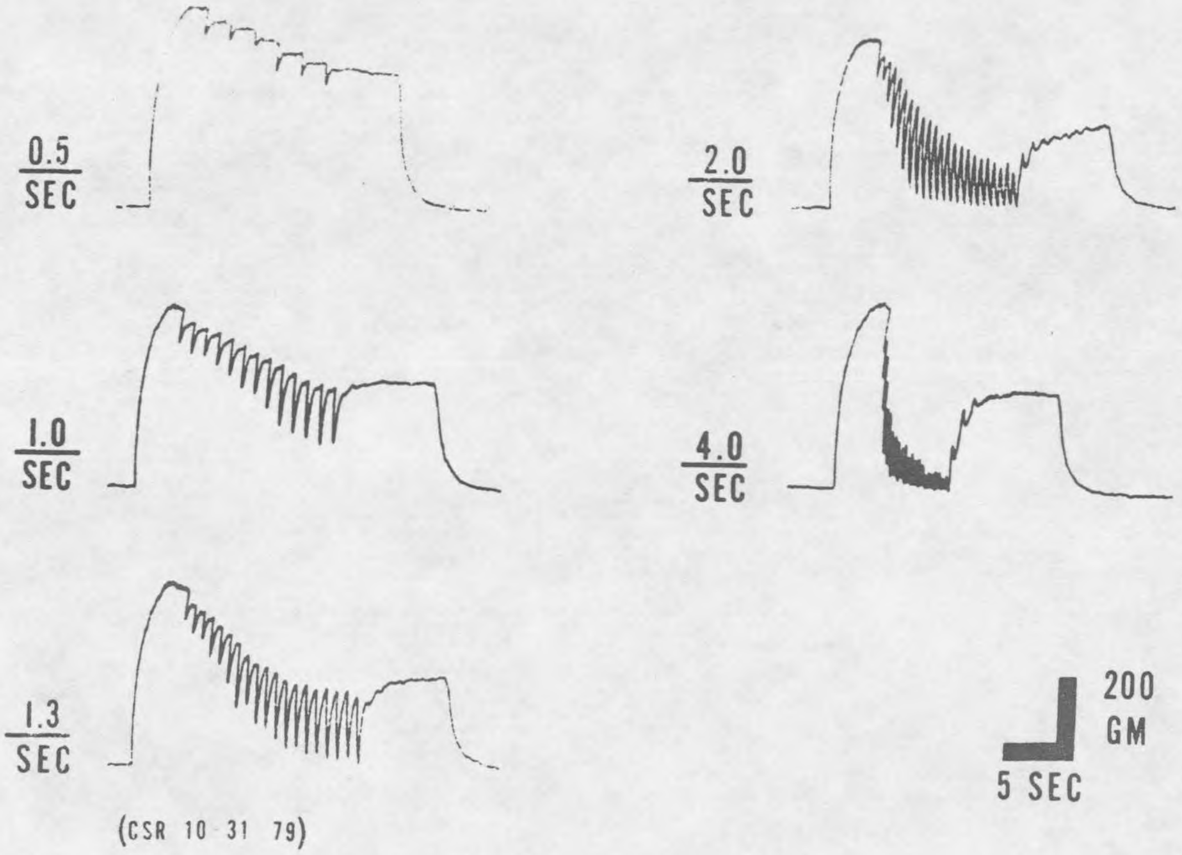

FIGURE 14. Effects of inhibitory stimulation of the right sciatic nerve on CERs evoked by repetitive stimulation. First, CERs were evoked by iterative stimulation (10 herz) of the left sciatic nerve. At the peak of the CER stimulation of the right sciatic was commenced. Different frequencies of right sciatic stimulation were used to inhibit the CER. In this preparation equivalent frequencies of excitatory and inhibitory stimulation led to complete inhibition of the CER. The inhibition was seen to sum at low frequencies of stimulation.

DISCUSSION

The results presented here can be divided into two separate but related considerations. The first is that the sensitivity of the CER is affected by various sensory inputs including mechanoreceptive, proprioceptive, and vestibular inputs from the brainstem. Many of the changes in excitability of the CER described here are consistent with previously described static righting and postural reflexes. The second consideration is that evoking CERs with single afferent volleys under certain conditions in these decerebrate cats offered an opportunity to study recruitment of reflex muscle tension in response to low frequencies of stimulation.

Previous descriptions of the CER have emphasized the difficulty in evoking a consistent response in acute decerebrate preparations (Creed et al., 1932). The present study indicates that CERs evoked in acute decerebrate cats may indeed be very excitable. In contrast to previous studies which have all indicated that single afferent volleys are incapable of evoking crossed extension in acutely decerebrated cats, it is shown here that CERs in decerebrate preparations can be evoked by single afferent volleys.

Related studies have described more excitable crossed extensor responses, but only with modifications of the decerebrate preparation (Forbes and Cattell, 1924; Matthes and Ruch, 1933). These studies described increased crossed extensor responses when either decerebrated animals were deafferented (Forbes and Cattell, 1924) or had their spinal cords transected subsequent to decerebration (Matthes and Ruch, 1933). Only in chronic spinal preparations, however, have single afferent volleys evoked brief crossed extensor twitches (Matthes and Ruch, 1933). Consistent crossed extension reflexes can also be evoked from unmodified midcollicular decerebrate cats, but only when the head of the preparation was rotated towards the side from which the CER was evoked (Pi-Suner and Fulton, 1929). No CERs were evoked by single afferent volleys in these preparations. Both tonic neck and labyrinthine sources may contribute to increased excitability of the CER, but Pi-Suner and Fulton avoided distinguishing between the two inputs (Pi-Suner and Fulton, 1929).

The present results indicate that the excitability of the CER is significantly affected by body position. CERs recorded from the right quadriceps are facilitated in animals placed on their right side. In this position single afferent volleys evoked CERs. No previous known reports have illustrated this response in acutely decerebrated animals. The significance of body position in affecting the excitability of the CER is further indicated by the high frequencies required to evoke even gradual recruitment when CERs were recorded with preparations on the left body surface. Previous reports had labelled this slow type of reflex recruitment as "addition latente" (Creed et al., 1932).

Previous studies on crossed reflexes may have not taken into consideration the effects of whole body position in determining the excitability of spinal reflexes in decerebrate animals (Eccles and Granit, 1929; Liddell and Sherrington, 1923; Perl, 1957; Sherrington, 1910). Specific methods in related studies indicated that initial placement of preparations was in a position unfavourable to the recording of extensor or crossed extensor reflexes in the limb from which responses were recorded (Ballif et al., 1925; Pi-Suner and Fulton, 1929).

Although the present methods and animal preparations which provide conditions where the responsiveness of the CER responses is augmented, the data also support previous descriptions of a more labile CER (Creed et al., 1932; Holmqvist, 1961; Liddell and Sherrington, 1923a; 1923b; Perl, 1957). CERs evoked by iterative stimulation were more susceptible to suprasegmental and segmental inhibitory inputs than flexion reflexes (Creed et al., 1932; Liddell and Sherrington, 1923a; 1923b). Rotation of the body or head away from the recorded side (chin left) and left forelimb flexion produced the most pronounced inhibition of the CERs evoked in the right quadriceps muscle. Activation of mechanoreceptors on the left side evoked some inhibition of CERs evoked by high frequency stimulation. All the described inputs inhibited the CER.

The labile nature of CERs evoked in decerebrate preparations may be the result of convergence of inhibitory inputs at different points in the CER path. Commissural interneurons in the ipsilateral to contralateral pathway, interneurons on the contralateral side, or motorneurons supplying extensor muscles may be affected independently or conjointly by various sensory or descending inputs. Although there is no way from this study to describe the specific neuroanatomical location of these facilitory and inhibitory inputs, one can speculate that all points in the CER pathway could be regulated. The response evoked will reflect the integration of regulatory inputs at any or all of these points in the reflex path.

The most consistent example of central modulation described here is the facilitation of the CER in the right quadriceps when animals were placed on their right side. Three considerations indicate that the change in the excitability of the CER is directly related to the "body righting on body response" described by Magnus (1926). First, in the absence of any stimulation, rotation of the animal preparations onto the right lateral body surface evoked an extension in both the right fore- and hindlimbs. The extensor rigidity in the left limbs was concurrently diminished. This reflex caricature has been described as the first overt action leading to the body on body righting response (Bard and Macht, 1958). The enhanced extensor tone in the right limbs parallels the augmented responsiveness of the CER evoked by single or repetitive stimuli. Second, the CER was consistently inhibited by placing weight (pressure) against the left body surface. No change in the static labyrinth inputs or tonic neck inputs could have been evoked by such stimuli since the body and head position remained constant. Thus such inhibition parallels previous descriptions of the body on body reaction which indicated a separate effect on postural tone determined by mechanoreceptive inputs (Beritoff, 1915; Magnus, 1926). Third, stimulation of the left sciatic in preparations initially placed on their left side evoked a a spontaneous and coordinated rotation to the right. This response likely represents a caricature of the righting reflexes characteristic of precollicular decerebrate preparations (Bard and Macht, 1958; Magnus, 1926).

The facilitation of extensor tone in the ipsilateral fore- and hindlimbs in these decerebrate cats evoked by rotation of the animals onto their side is consistent with features of both tonic neck and vestibulospinal reflexes. The increased tone in the extensor muscles of the right limbs and decreased tone in the left limbs of these preparations is consistent with previous reports indicating that static tilt to one side evokes extension in the ipsilateral limbs and flexion in the contralateral limbs (Bard and Macht, 1958; Magnus, 1926). However, decerebrate cats which have had their high cervical afferents transected or have had their heads cast to eliminate inputs from the neck afferents show a reciprocal pattern (ipsilateral flexion and contralateral extension (Lindsay et al., 1976; Schor and Miller, 1981). These results are difficult to reconcile with a strictly vestibular control of body on body reflexes. Previous descriptions of vestibulospinal reflexes (Bard and Macht, 1958; Mountcastle, 1980) indicated that facilitation of extensor tone on the side of the animal tilted down is usually accompanied by rotation of the head to the left, however, no rotation of the head to the left was observed concurrent with rotation of the body to the right. This suggests that vestibulospinal inputs alone fail to account for the basis of the entire response. A vectorial summation of inputs from static vestibular inputs and tonic neck inputs likely account for the complete response (Ezure and Wilson, 1983; Wilson et al., 1984).

The changes in the excitability of the CER evoked by changes in the body position, however, are consistent with other features of vestibular control of spinal reflexes. Previous studies have largely supported that vestibular inputs evoked by static tilt to one side directly facilitate ipsilateral motorneurons supplying extensor muscles (Gernandt and Thulin, 1953; Lund and Pompeiano, 1968; Wilson and Yoshida, 1969) or indirectly facilitate interneurons in the ventral laminae of the spinal cord which supply extensor motorneurons (Bruggencate and Lundberg, 1974; Erulkar et al., 1966; Wilson and Yoshida, 1969). The present results support a dominant excitatory input to extensor muscles in the ipsilateral limbs. Since the CER is a polysynaptic reflex (interneurons) and vestibulospinal projections to the lumbar cord also terminate on interneurons of the ventral horn (Nyberg-Hansen and Mascitti, 1964; Wilson and Peterson, 1981), some interneurons contributing to the CER may also receive convergent input from vestibulospinal sources. Another study has indicated such a facilitory convergence from contralateral primary afferents onto interneurons responding to vestibulospinal stimulation (Bruggencate and Lundberg, 1974).

Facilitation and inhibition of the CER evoked by rotations of the head in these experiments are consistent with classic descriptions of the neck on body righting reflexes (Bard and Macht, 1958; Beritoff, 1915; Magnus, 1926) and the results of more recent studies which distinguish between static labyrinth and tonic neck reflexes (Ezure and Wilson, 1983; Lindsay et al., 1976; Schor and Miller, 1981; Wilson et al., 1984). The changes in the excitability of the CER evoked by the head rotations performed in this study could be affected by inputs from both static labyrinth and tonic neck inputs (Ezure and Wilson, 1983; Lindsay et al., 1976). The CER, however, appears more sensitive to inputs related to the tonic neck reflexes. The CER produced in the right quadriceps is facilitated or inhibited by rotation of the head to the right or left, respectively. These changes in the response of the CER are more consistent with the patterns of activity evoked by afferents mediating the tonic neck reflexes (Ezure and Wilson, 1983; Lindsay et al., 1976; Wilson et al., 1984). A reciprocal pattern of response would have indicated a predominant influence from the labyrinths.

A brief facilitation of the CER evoked during head rotations was occasionally encountered and is consistent with previous reports of phasic responses occurring in conjunction with static inputs from the labyrinthes and tonic neck afferents (Ezure and Wilson, 1983; Wilson et al., 1984). This transient facilitation in the present study occurred when the head was rotated in either direction, but only during the actual movement of the head. This is consistent with the involvement of phasic afferent input originating from the large number of proprioceptors in the neck muscles (Abrahams, 1977; Richmond and Abrahams, 1979) or from otolith receptors responding to sudden linear accelerations (Anderson et al., 1977). This type of a response has been related to the functional ability of animals to brace against sudden unexpected falls (Watt, 1976). On these occasions where phasic extension was observed the tonic reflex effect reappeared if the rotation of the head was maintained for several seconds.

The changes in excitability of the CER evoked by positioning of the head also indicate that not all inputs related to neck on body reflexes are effective in altering the excitability of the CER. Dorsiflexion and ventriflexion which typically evoke bilateral responses in the forelimbs and hindlimbs (Magnus, 1926) do not evoke a change in the excitability of the CER. This result suggests that postural or righting reflexes which typically evoke reciprocal responses in the limbs seem more effective in changing the excitability in the CER pathway. Although it can not be ascertained from this study, bilateral postural responses may involve bilateral connections in the reticular formation from both labyrinth and neck afferents which are unable to strongly affect reciprocal type reflexes (FR-CER) evoked in the spinal cord.

The inhibition of the crossed extensor reflex evoked by flexion of the left forelimb in the present study is consistent with previous descriptions of propriospinal inputs affecting the excitability of extensor muscles in decerebrate animals (Pi-Suner and Fulton, 1927). The convergence of reflex paths indicated by this response are also consistent with the relationship between reciprocal locomotor patterns in both fore- and hindlimbs (quadrupedal locomotion) and reciprocal segmental reflexes (FR and CER) suggested in previous studies (Jankowska et al., 1967; Grillner, 1981). The present results also parallel classical studies which described modulation of the CER by neck and limb proprioceptive inputs (Beritoff, 1915; Pi-Suner and Fulton, 1929). Although there is no way in the present procedures to define the anatomical or physiological mechanisms involved in this interlimb response, these results suggest a convergence of proprioceptive inputs onto common elements of the CER pathway. Studies which show convergence of proprioceptive and cutaneous afferents on common interneurons in the ventral or intermediate horn interneurons of the spinal cord furnish indirect support for coordination of reflexes by both proprioceptive and cutaneous inputs (Kolmodin, 1957; Wall, 1967).

The changes in excitability of the CER evoked by head rotation (tonic neck reflexes) or forelimb manipulation are consistent with activity associated with both long descending propriospinal (bulbospinal correlative system) (Lloyd, 1941) inputs or short propriospinal inputs to the hindlimbs originating from the neck (Kenins et al., 1978) and the forelimbs (Gernandt and Shimamura, 1961; Shimamura and Livingston, 1963). The present results can not be used to distinguish between long and short latency propriospinal effects, although previous studies indicate that both systems are active in decerebrate preparations (Gernandt and Shimamura, 1961; Kenins et al., 1978; Shimamura and Livingston, 1963). The strength of the inhibitory action of left forelimb flexion on the right hindlimb CER coincides with previous reports of strong descending inputs from the forelimbs to the hindlimbs in decerebrate animals (Gernandt and Shimamura, 1961).

The clonus observed and recorded in the present decerebrate cats is consistent with the classical model of clonus described by Denny-Brown (1929). Although there was no way to specifically ascertain the origin of the clonus in these preparations, the frequency of rhythymical activity of the large extensors suggests a relation to massive discharge of synchronized myotatic reflexes in the extensor muscles (Denny-Brown, 1929).

The clonus or locomotor responses evoked by intense stimulation in this study can be indirectly related to reports indicating a relationship between the polysynaptic reflexes of flexion and crossed extension to locomotion and pattern generation in the spinal cord (Jankowska et al., 1967a; 1967b). In those studies spinal cats which have been administered DOPA exhibit long latency and prolonged flexion and crossed extension reflexes which are associated with locomotor responses. Those studies infer that polysynaptic reflex paths are associated with the intrinsic spinal organization of locomotion (Jankowska et al., 1967b). Since clonus or locomotion in the present study was often evoked concurrent with stimuli meant to evoke the CER, these activities could have been recruited through a common path involving polysynaptic reflexes and pattern generation.

The clonic activity evoked from decerebrate cats in this study could represent a part of the complete locomotor pattern generated by the remaining Ia afferent input which is not inhibited by reticular inputs (Holmqvist and Lundberg, 1961). The complete expression of a coordinated locomotor response may require attenuation of reticular inhibition of polysynaptic FRA paths by spinal section and/or administration of DOPA (Grillner, 1981). Although the present experiments cannot ascertain the specifics of decerebrate control of locomotor reflexes, previous reports indicate that the control of polysynaptic reflexes by reticular inputs may be exerted through modulation of the afferent inputs to the spinal cord (PAD or presynaptic inhibition) (Carpenter et al., 1963; 1965) or via direct synaptic action on interneurons mediating polysynaptic reflexes (Engberg et al., 1968a; 1968b). Since normal locomotion involves reciprocal reflexes in paired limbs, release of reciprocal polysynaptic paths from reticulospinal inhibition would likely disinhibit the nocifensive reflex responses, as well as locomotor activity.

Although locomotor patterns were evoked by iterative stimulation of the left sciatic in both cats and ungulates (McMillan and Koebbe, unpublished observations) clonic activity was more prevalent in decerebrate cats. Distinct locomotor responses (walking motions) evoked by stimulation of afferents were more often seen in anemically decerebrated lambs (McMillan and Koebbe, unpublished observations). This activity was often seen after production of flexor and crossed extensor reflexes. Such clonic or locomotor responses in decerebrate lambs and cats may reflect fundamental differences in motor control in these phylogenetically different species. Ungulates posess a limited specialization of the forelimbs and are capable of functional locomotion at an early stage of development. In contrast cats (carnivores) utilize their forelimbs for more than a locomotive function and develop coordinated locomotion at a later stage of development. Ungulates may require less control of locomotive patterns as a result of the lesser degree of specialization in the limbs. In lieu of central control of the intrinsic locomotor systems of the spinal cord (see Grillner, 1981) locomotion in ungulates may be more predisposed to control by afferent input. In contrast the predisposition for clonus in cats suggests a stronger control of coordinated locomotor responses from higher brain structures. Removal of central modulation from more rostral CNS inputs may permit only a caricature of a locomotor or patterned response, or clonus.

Until the present description of CERs evoked by low frequency stimulation, the CER has proven too labile to examine recruitment of nocifensive reflexes to individual or trains of low frequency stimuli (Creed et al., 1932; Holmqvist, 1961). The discovery that a CER could be evoked by a single stimulus with the body placed in the appropriate position enabled the examination of reflex summation produced by trains of low frequency stimulation.

Two features of the crossed extensor responses were indicative of prolonged central summation. First, the duration of individual CERs evoked by a train of low frequency stimuli increases with each succeeding stimulus. The brief initial portion of a CER remained largely the same from stimulus to stimulus. However, with each succeeding stimuli a gradual recruitment of a longer latency response ("spike-hump") was observed. The magnitude of prolonged central summation is dependent on the frequency of stimulation used to evoke CERs. Although prolonged activity could be seen when interstimulus intervals of greater than 7 seconds were used, the minimal interval required for summation varied in different experiments. In all experiments, however, stimulus intervals of several seconds were still sufficient to produce central summation.

These indications of prolonged spinal excitation in the CER are consistent with the analysis used in classical studies of reflex summation (Sherrington, 1921; Sherrington and Sowton, 1915; Matthes and Ruch, 1933; Eccles and Sherrington, 1930). These previous investigations also suggested the existence of central excitatory states in the spinal cord which were responsible for prolonged reflex activity. The central excitatory state described in classical studies was also strongly influenced by the the intervals between stimuli (frequency) (Sherrington, 1921). The results of the present experiments are also consistent with those previous reports which indicated that the duration of the central excitatory state is not related to effects of reiterative activation of afferents by a single stimulus (Eccles and Sherrington, 1930). The prolonged discharge (central excitatory state) in the CER lasted as long as 7 seconds in some preparations in the present investigation. This duration indicates that this prolonged summation is not mediated by the arrival of multiple afferent volleys and is consistent with prolonged central excitation in FR pathways (Sherrington, 1921).

The summation of activity in the CER extends previous studies on reflex summation to noxious inputs (Iwamoto et al., 1980; Price, 1972). These studies indicate that the characteristics of nocifensive reflex summation closely parallel summation of activity in the spinal cord related to recruitment of perception of noxious stimuli. Similar frequencies of stimulation of "pain" afferents (C fibers) in a recent report (<0.3 hz) show parallels in the summation (or "windup") of second pain and a long latency and prolonged flexion reflex

(Schouenborg and Sjolund, 1983). Another recent report indicates that in contrast to the FR, CERs evoked in decerebrate animals exhibit an even more prolonged summation than that described for the flexion reflex (Moudy and McMillan, 1982). This is evident in the present results which show prolonged effects at even lower frequencies (0.14 hz) of stimulation than that required to prolong the flexion reflex (>0.3 hz) (Iwamoto et al., 1980; Price, 1972; Schouenborg and Sjolund, 1983).

The double response seen in CERs evoked by single stimuli (a short latency spike and a delayed hump) is in many ways similar to double responses in dorsal horn cells evoked by stimulation of low and high threshold cutaneous afferents (Mendell, 1966; Price, 1972; Price et al., 1971: Price and Wagman, 1970; Wagman and Price, 1969). The recruitment of a prolongated discharge is recorded from dorsal horn cells (Laminae 4-6) when A-delta or C afferents are stimulated at frequencies >0.33 hz. (Price, 1972; Wagman and Price, 1969). Crossed extensor responses evoked by a series of low frequency stimuli also show a gradual recruitment of the late reflex discharge. Although the present results can distinguish no direct correlation between dorsal horn responses and recruited activity in the CER, it is interesting to speculate that recruitment in the CER evoked by low frequencies of stimulation is related to the "windup" discharge in dorsal horn cells evoked by similar low frequencies of stimulation of C afferent fibers.

The flexion reflex has also been shown to have early and late responses evoked by stimulation of mixed afferents (Eccles and Lundberg, 1959b; Holmqvist and Lundberg, 1961; Iwamoto et al., 1980;

Price, 1972; Schouenborg and Sjolund, 1983). Like the short latency CERs described in the present study, the early FR discharge has been associated with stimulation of low threshold Ia afferents (Holmqvist and Lundberg, 1961) and does not sum with low frequencies of stimulation. The long latency CERs may be related to the polysynaptic reflex paths evoked by stimulation of higher threshold FRAs (Eccles and Lundberg, 1959; Jankowska et al., 1967a). Schouenborg and Sjolund (1983) have also shown that the recruiting discharge of the FR is related to the longer latency polysynaptic flexion reflexes. It is interesting to speculate that the windup in late CERs evoked by low frequency stimulation may be related to the enhanced polysynaptic FRs evoked by similar frequencies of A delta or C afferent stimulation (Price, 1972; Schouenborg and Sjolund, 1983).

Current investigations support the importance of the afferent input in determining the excitability of the CER (McMillan, Hannon, Stevenson, and Koebbe, unpublished observations). The excitability of the CER evoked by brief trains of stimuli of the ipsilateral sciatic nerve is augmented when the limb from which the response is elicited is deafferented. This result is consistent with previous reports indicating increased excitability of the CER in deafferented decerebrate preparations (Forbes and Cattell, 1924; Eccles and Granit, 1929). The quality and magnitude of the afferent input to the contralateral spinal cord may affect the CER as has been previously described in studies with reflex reversals (Rossignol and Grillner, 1978; Rossignol and Gauthier, 1980).

Summation in the CERs evoked by low frequency stimulation also suggests a relationship with recruitment of sensation. Second pain which is evoked by noxious C afferent stimulation sums with similar low frequencies of stimulation (Iwamoto et al., 1980; Price, 1972). A related clinical study in a patient with Tabes also showed that a prolonged flexor withdrawal reflex was directly associated with the perception of second pain (Ashby, 1949). These studies are consistent with a more direct relationship between the painful sensation and reflex responses evoked by stimulation of noxious afferents.

Inhibition of the CER evoked by low frequency stimulation of the ipsilateral sciatic nerve, as seen here, is consistent with classical concepts of reflex organization. Stimulation of the right sciatic evokes a FR in opposition to the CER evoked by stimulation of the left sciatic nerve. Such CERs are inhibited by low frequency stimulation of the right sciatic nerve. Similar methods in classical studies also indicated that the CER is much more susceptible to inhibition by such opposing stimuli than the spinal flexion reflex (Liddell and Sherrington, 1923a; Liddell and Sherrington, 1923b). This result is related to the type of preparation utilized. CERs facilitated by appropriate positions in this study seem more resistant to complete inhibition than previously described (Eccles and Granit, 1929; Liddell and Sherrington, 1923a; 1923b). Complete inhibition of the CER could only be evoked by nearly equivalent stimulation of the contralateral and ipsilateral sciatic nerve. Although low frequency stimulation failed to completely inhibit the CER, the inhibition showed a recruitment with very low frequencies of stimulation. This result parallels classical studies indicating that inhibition is also dependent on stimulus frequency and capable of prolonged central summation (Liddell and Sherrington, 1925; Sherrington, 1925).

Part of the reason that CERs could be evoked by single shocks in these decerebrate preparations may be related to modifications in the reticular control of spinal reflexes. The previous discussion of static righting reflexes and postural mechanisms indicate how reticular inputs can enhance the excitability of the CER in decerebrate preparations. It can be assumed that positioning of the animal in a configuration facilitating CERs may diminish the reticular suppression of polysynaptic reflexes usually encountered in the decerebrate preparation (Holmqvist and Lundberg, 1961; Holmqvist, 1961; Eccles and Lundberg, 1959). An extension of the present investigation might elaborate on the basis of this control by establishing whether positioning of the animal leads to changes in the control of specific primary afferents or interneurons of the dorsal or ventral horn.

This study did not consider either of the two previously described methods by which the reticular formation may control reflex responses. Modulation of the CER may occur by control of primary afferent input or direct control of interneurons in the reflex path. It can only be speculated that body position varies the reticular inputs to the spinal cord leading to the variations in the excitability of the CER. The present results, however, suggest that afferent input capable of evoking polysynaptic reflexes (high threshold afferents) were less inhibited by appropriate body position.

These changes in reticular control of spinal reflexes are also consistent with behavioural responses of the animal related to the body on body, neck on body, and postural reflexes also known to originate in the brainstem. By diminishing the reticular inhibition to one side of the spinal cord interneurons may gain access to more direct inputs from segmental afferent nerves. In such a case the reflex (CER) would more closely resemble responses evoked in spinal animals (Matthes and Ruch, 1933).

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