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SUPRASPINAL AND SEGMENTAL CONTROL OF STATIC AND DYNAMIC γ-MOTONEURONES IN THE CAT

BY

STEN GRILLNER

GÖTEBORG 1969

Dissertation
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STEN GRILLNER

GÖTEBORG 1969

to Lena

CONTENTS

This thesis mainly constitutes a summary of the following articles:

I. Grillner, S., T. Hongo and S. Lund, Descending monosynaptic and reflex control of γ-motoneurones. Acta physiol. scand. 1969. In press.

II. Bergmans, J. and S. Grillner, Changes in dynamic sensitivity of muscle spindle primary endings induced by DOPA. Acta physiol. scand. 1968. 74. 629-636.

III. Bergmans, J. and S. Grillner, Reciprocal control of spontaneous activity and reflex effects in static and dynamic γ-motoneurones revealed by an injection of DOPA. Acta physiol. scand. 1969. In press.

IV. Bergmans, J. and S. Grillner, Monosynaptic control of static γ-motoneurones from the lower brain stem. Experientia 1968. 24. 146-147.

V. Grillner, S., The influence of DOPA on the static and dynamic fusimotor activity to the triceps surae of the spinal cat. Acta physiol. scand. 1969. In press.

GENERAL INTRODUCTION

The "final common path" for motor regulation, i. e. the α-motoneurone (Sherrington 1904) is strongly influenced from segmental reflex paths originating from various kinds of receptors (cf. Creed, Denny-Brown, Eccles, Liddell and Sherrington 1932). Of particular importance is the muscle spindle which has large afferent fibres with monosynaptic excitatory effects to motoneurones supplying its own muscle (cf. Lloyd 1943, Granit 1950). These afferents provide the afferent path for the well-known stretch reflex (Liddell and Sherrington 1924).

Onanoff's finding (1890) of an efferent nerve supply to the muscle spindle gave this receptor a unique position among muscle receptors. The subsequent analysis by Leksell (1945) and Kuffler, Hunt and Quilliam (1951) showed that the muscle spindle of the cat indeed has a motor supply of its own via nerve fibres of small calibre, the γ-efferents. The central control of the γ-motoneurones is exerted via different segmental reflex paths (Hunt 1951, Kobayashi, Oshima and Tasaki 1952) and from various supraspinal structures (Granit and Kaada 1952, Eldred, Granit and Merton 1953, Granit and Holmgren 1955); parallel effects could often be evoked in α- and γ-motoneurones but often with lower threshold in the latter. The γ-control determines the discharge rate in the muscle spindle afferents during dynamic and static conditions in the muscle and is thereby one important factor determining the excitability level of the α-motoneurones (cf. Granit 1955, 1968, Matthews 1964).

In 1962 it was shown that the γ-efferents are of two kinds (Jansen and Matthews 1962a, Matthews 1962), one type controlling mainly the dynamic sensitivity of the primary endings (Ia afferents) and the other the discharge rate, and presumably also the static sensitivity of the primary endings (Jansen and Matthews 1962a, Brown, Lawrence and Matthews 1969) and in addition the activity in secondary endings (group II afferents) (Appelberg, Bessou and Laporte 1966).

Rather selective effects on static and dynamic γ-motoneurones can be produced from different central nervous structures. Thus, stimulation of the anterior lobe of the cerebellum gives a depression of the activity mainly in dynamic γ-motoneurones (Jansen and Matthews 1962 a). A selective activation of dynamic γ-motoneurones to certain muscles can be evoked from the mesencephalic tegmentum (Appelberg 1963, Appelberg and Emonet-Denand 1965), and from the pyramidal tract (Vedel 1966). Effects on static γ-motoneurones are obtained from the caudate nucleus (Vedel and Paillard 1965) and from certain regions of the cerebral cortex outside the motor area (Baudevin and Vedel 1967).

Certain differences between the two kinds of γ-motoneurones appear to exist also at the segmental level (Jansen 1966). Thus in the spinal cat, dynamic but not static γ-motoneurones are spontaneously active and reflexly excitable (Alnaes, Jansen and Rudjord 1965). On the other hand, after an injection of DOPA, which is assumed to liberate noradrenaline from descending noradrenergic fibres in the spinal cat, static γ-motoneurones to flexors acquire a resting discharge and can be reflexly activated (Grillner, Hongo and Lundberg 1967). The cited studies on the selective control of dynamic and static γ-motoneurones have all been obtained by indirect methods (recording of muscle spindle afferents) and it is difficult to draw conclusions regarding the synaptic linkage of various systems influencing these neurones.

The detailed investigations of the control of γ-motoneurones have been greatly handicapped by the difficulty in obtaining intracellular records or applying a monosynaptic test technique. In the present studies γ-motoneurones have been investigated by intra- or extracellular recordings in the spinal cord or by the activity in single efferents in peripheral nerve filaments and also indirectly through spindle afferents. The aim has been to elucidate some aspects of

I. The segmental control of static and dynamic γ-motoneurones via different reflex paths.

II. The descending control of static and dynamic γ-motoneurones via

a) two fast conducting descending systems from the brain stem. i. e. the vestibulospinal tract and fibres coursing in the medial longitudinal fascicle (MLF) presumably of reticular origin and

b) the "noradrenergic reticulospinal system"

METHODOLOGICAL CONSIDERATIONS

Papers I—V have been concerned with a study of γ-motoneurones supplying the left hindlimb of the cat. The detailed methodological descriptions are given in the different papers.

In papers I, III—V the control of single γ-motoneurones has been investigated and only one point of general interest will be considered here, the identification of γ-motoneurones.

In paper I the γ-motoneurones intracellularly recorded could be identified by the following criteria

1) antidromic invasion from one muscle nerve should occur without graded prepotentials,

2) the conduction velocity of the efferent responsible, should be within the range 20—45 m/sec (cf. Eccles, Eccles, Iggo and Lundberg 1960),

3) the location of the cell should be within the appropriate motor nucleus (Eccles et al. 1960, Nyberg-Hansen 1965),

4) no monosynaptic excitation should be evoked from group Ia afferents (Hunt and Paintal 1958, Eccles et al. 1960),

5) the threshold for the efferent fibre, should be several times above that for group Ia afferents or α-efferents (Leksell 1945).

A few cells were recorded when the ventral roots were cut and then the identification rested on criteria 1, 3—5. Particular attention was then paid to criterion 4, and the lack of Ia EPSP was checked by stimulation of the dorsal roots. In the extracellular material the activation of a cell with a fixed latency was taken to indicate that it was antidromically activated; criteria 2—5 could then be applied. If such a cell was later impaled it was always found to be a γ-motoneurone by the above criteria.

In papers III—V the γ-motoneurones had to be investigated for a long time and therefore the γ-efferents were recorded in peripheral nerve filaments. By stimulation of the intact ventral root(s) the number of γ-efferents in a filament could be determined; the isolation of γ-efferents did not depend on the presence of a resting discharge. The identification of an efferent as being of the "γ-type" rested on criteria 2, 4, 5. The isolation of only one, or sometimes two easily distinguished γ-efferents, was performed by making successive lesions in the ventral root until only one (two) γ-efferent was in connexion with the spinal cord.

REFLEX EFFECTS FROM PRIMARY AFFERENTS

A. Group I afferents

By graded stimulation of muscular nerves a selective activation of group I afferents can be obtained, and in the nerves to the thigh muscles even a separation of a Ia and a Ib component (Bradley and Eccles 1953, Eccles, Eccles and Lundberg 1957 a). In five extensor γ-motoneurones (paper I) IPSPs could be evoked at group I strength. This effect was found in some γ-motoneurones in which the ventral roots were cut, thus excluding the possibility of antidromically evoked recurrent inhibition from α-fibres (Ellaway 1968, Brown, Lawrence and Matthews 1968 a). The shortest latency of these IPSPs was 1.8 msec, which is hardly compatible with an orthodromic activation of α-motoneurones through which recurrent inhibition may be evoked in these γ-motoneurones. Furthermore the IPSPs evoked from recurrent collaterals in α-motoneurones have a duration of approximately 50 msec (Eccles, Fatt and Koketsu 1954) whereas the group I IPSP in γ-motoneurones have a much shorter duration. Hence it is more likely that the synaptic effects are evoked via reflex paths to γ-motoneurones. The results do not allow a conclusion of whether the origin is group Ia or Ib fibres. The segmental latencies and the pattern of distribution in the few cells recorded are similar to the Ib pattern found in α-motoneurones (Eccles, Eccles and Lundberg 1957 b). Furthermore in paper V, a gastrocnemius γ-motoneurone did receive synaptic effects from afferents activated at "Ib-strength". From electrical stimulation no effect clearly ascribable to group I afferents has been reported (cf. however Eccles, Eccles, Iggo and Lundberg 1960, Voorhoeve and van Kanten 1962). On selective activation of group Ia afferents by vibration, however, a marked inhibition is evoked in spontaneously discharging γ-efferents (Brown, Lawrence and Matthews 1968 b). Their published results do not allow an estimate of the latency, and a conclusion cannot be drawn whether these effects are mediated via segmental reflex paths to γ-motoneurones or indirectly via activation of α-motoneurones and recurrent collaterals, or through reflex paths involving supraspinal structures.

Hunt (1951) and Eldred, Granit and Merton (1953) reported autogenetic inhibition in γ-motoneurones in response to muscle stretch in the decerebrate cat. In a subsequent study, Hunt and Paintal (1958) could not confirm these results in the spinal cat. However, these two preparations differ in two respects: 1) static γ-motoneurones are spontaneously active in the decerebrate (Jansen and Matthews 1962 a, b) but not in the spinal preparation, in which only the dynamic have a resting discharge (Alnaes, Jansen and Rudjord 1965, paper II); 2) a tonic stretch reflex occurs in the decerebrate but not in the spinal preparation (Liddell and Sherrington 1924). The different findings on decerebrate and spinal cats would be explicable if the autogenetic inhibitory effects were exerted only on static γ-motoneurones. If the group I inhibition (paper I) is responsible, it is relevant that of four γ-motoneurones tested for descending effects, all received monosynaptic EPSPs, which suggests that they are of the static type (paper I, IV, V). It is also relevant that the group Ib afferents have a high sensitivity for active, but not for passive tension (Jansen and Rudjord 1964, Houk and Henneman 1967). The absence of autogenetic inhibition in the spinal, but its presence in the decerebrate preparation may be correlated with the fact that a stretch reflex occurs in the latter but not in the former state (Liddell and Sherrington 1924). Accordingly it may be possible to explain the findings by Hunt (1951) and Hunt and Paintal (1958) without any postulate regarding a selection in destination to static and dynamic γ-motoneurones.

B. Group II afferents

Stimulation of muscle nerves at strength of 2.5 to 8 times threshold of the most excitable fibres activates the fibres conducting in the group II range (Eccles and Lundberg 1959). At this stimulation strength excitatory effects could be evoked in flexor γ-motoneurones classified as static and dynamic (paper III) and also in gastrocnemius γ-motoneurones excitatory or inhibitory reflex effects could be revealed (paper V). These effects could be evoked from nerves to flexors and extensors working at different joints. In this unanaesthetized spinal preparation corresponding effects can occasionally be evoked in α-motoneurones (cf. paper V). Although the majority of group II fibres probably have secondary endings from the muscle spindles (cf. Hunt 1954) the presence of other fibres of this diameter has been shown by Paintal (1960) and Barker (1967). Thus the presence of "group II effects" does not necessarily imply that they are caused by secondary endings from the spindle. However, Laporte and Bessou (1959) have shown that in a spinal preparation, in which conduction in group I afferents had been blocked, inhibitory effects are evoked on muscle stretch in extensor and excitatory effects in flexor α-motoneurones. Although reflex effects from smaller diameter fibres cannot be entirely excluded the most likely explanation is that these reflex effects are due to activation of secondary endings, which hence are assumed to give effects conforming to the flexor reflex pattern (Sherrington 1910). These results are in accordance with the results obtained with electrical stimulation of peripheral nerves (Laporte and Lloyd 1952, Eccles and Lundberg 1959). However, excitatory effects to extensors can also sometimes be encountered (Holmqvist and Lundberg 1961, Wilson and Kato 1965). Since the secondary endings are under efferent control and have a signal lineraly related to muscle length, these seemingly nonspecific reflex connexions (cf. Matthews 1964) to α- and presumably also γ-motoneurones are rather puzzling (cf. also page 24). However, it might be pertinent to note that the frog, which has no specific motor supply to the spindles (Katz 1949), only has one type of afferent corresponding presumably to the primary ending. The significance of the secondary endings in the cat might not be related to a delicate spinal reflex pattern but in mediating information related to muscle length and static γ-bias to supraspinal structures.

C. Cutaneous afferents and group III muscular and joint afferents

In Hunt's (1951, cf. also Kobayashi, Oshima and Tasaki 1952) original description of the reflex activation of γ-motoneurones he reported that these efferents as a rule followed the pattern of flexor-crossed extensor reflexes of α-motoneurones (Sherrington 1910). Numerous exceptions to this pattern were, however, found in a subsequent study by Hunt and Paintal (1958). Their conclusion that the reflexes to α- and γ-motoneurones differ in several respects deserves some further discussion.

In confirmation of several previous studies, γ-motoneurones to flexors (paper III) were found to receive excitation from ipsilateral nerves. All γ-efferents studied could be reflexly activated by single volleys, dynamic γ-motoneurones more effectively than static (for identification see page 17). The analysis of their reflexes was aided by the comparison of effects before and after DOPA. An injection of DOPA decreased the reflex activation of dynamic and increased the reflex activation of static γ-motoneurones (paper III). These opposite effects may be a consequence of the corresponding changes in the resting activity; an alternative possibility is that the effects were mediated by two different short latency reflex pathways (cf. Fig. 10 paper III). Reflex effects have previously only been demonstrated in a part of the extensor γ-motoneurone population (Hunt and Paintal 1958), but with the aid of DOPA it was possible to demonstrate short-latency reflex effects in all gastrocnemius γ-motoneurones investigated. Hence it is postulated that both static and dynamic γ-motoneurones can be influenced. The detailed analysis of these reflex effects is difficult since both excitatory, inhibitory and mixed effects could be evoked from ipsilateral nerves. There were some discrepancies between intra- and extracellular findings, which rather would be expected (paper I). Since ipsilateral excitatory effects were common in extensor γ-motoneurones (I, V), it can be concluded that the reflex pattern is more complex than the classical flexor-crossed extensor reflex pattern. This confirms the previous results by Eldred and Hagbarth (1954), Hunt and Paintal (1958), Alnaes, Jansen and Rudjord (1965) and Jansen and Rudjord (1965).

However, the reflex effects to α-motoneurones from these afferents also diverge from this reflex pattern (Creed, Denny-Brown, Eccles, Liddell and Sherrington 1932, Hagbarth 1952); after Hunt and Paintal's (1958) report detailed information concerning these effects have been obtained. The crossed reflex actions to α-motoneurones in the spinal unanaesthetized cat are excitatory to extensors in about 50 % of the preparations, in the remainder they are inhibitory or mixed (Holmqvist 1961). From ipsilateral high threshold muscle afferents excitatory effects can often be encountered in extensor α-motoneurones (Lundberg, personal communication, Holmqvist and Lundberg 1961, Wilson and Kato 1965). From cutaneous afferents excitatory or mixed effects are generally evoked in α-motoneurones (triceps surae) supplying fast motor units, while inhibitory effects dominate in slow motor units (Bruggencate, Burke and Jankowska, unpublished). The complex organization and the fact that there are two types of α-motoneurones with different reflex effects within the same muscle renders a conclusion regarding an α-γ-linkage in reflex effects to the gastrocnemii very difficult. Reflexes to foot muscles from the pad can also diverge from the flexor reflex pattern (Engberg 1964) in a similar way to fusimotor reflexes to these muscles (Hunt and Paintal 1958).

The analysis of reflex effects evoked from repetitive nerve stimulation at different frequencies were of particular interest because of the previous findings (with indirect methods) by Alnaes, Jansen and Rudjord (1965) that reflex activation of dynamic but not static γ-motoneurones could be obtained in the spinal cat by repetitive nerve stimulation (40 pps). γ-motoneurones with a resting discharge were further accelerated with increasing rate of stimulation. On the other hand, units with no spontaneous activity could often be discharged at low stimulation frequencies (paper

III, V), but at higher rates they were inhibited. With the frequency employed by Alnaes, Jansen and Rudjord (1965) only γ-efferents with a resting discharge were influenced and not the other group (paper III, V). These findings are relevant in relation to the problem of whether or not the short-latency reflex effects to static and dynamic γ-motoneurones are mediated by the same reflex pathway (cf. paper III), and were also an important criterion in the classification of cells as dynamic or static (cf. below).

Adequate activation of the skin and underlying tissues could, in the present low spinal preparation (paper III, V), sometimes reflexly influence γ-motoneurones from a receptive field extending from the level of the spinalization to the most caudal part of the tail (paper V) including afferents from the skin, muscle tissues (activated by pressure or pinching of the muscle), the periosteum and the bladder; thus by unspecific stimuli from a very large receptive field that is unexpected for a system dealing with motor control. Increasing evidence has, however, accumulated that the descending control of α-motoneurones from e. g. the pyramidal and the rubrospinal tract (Lundberg and Voorhoeve 1962, Hongo, Jankowska and Lundberg 1969) is exerted through a facilitation or inhibition of the interneurones of reflex arcs providing an excitatory or inhibitory impingement of the cells. The functional significance of these large receptive fields might be to provide a background for the descending control, which will "rule" through an inhibition or facilitation of the reflex paths.

It should be emphasized that even if the above explanation is correct it does not exclude the presence of specific and very delicate spinal reflex pathways to γ-motoneurones.

D. Recurrent inhibition

In four of nine extensor γ-motoneurones, tentatively classified as being of both the dynamic and the static type (paper V), recurrent inhibitory effects were revealed in confirmation of the reports of Ellaway (1968) and Brown, Lawrence and Matthews (1968 a). The important problem whether the recurrent inhibitory effects are exerted in parallel in α- and γ-motoneurones remains to be solved.

E. $\alpha-\gamma$ linkage?

What is now the position with respect to an α-γ-linkage in the organization of spinal reflex pathways? The only firmly established difference between connexions to α- and γ-motoneurones is the lack of monosynaptic excitatory connexions from group Ia afferents in the latter (Hunt and Paintal 1958, Eccles et al. 1960). The effects from group I afferents offer a particularly interesting problem. It has not yet been established if the group I IPSPs in γ-motoneurones are evoked from muscle spindles or Golgi tendon organs. Should the latter receptor turn out to be responsible it still remains to be shown if the linkage is limited to static γ-motoneurones.

The complex reflex pattern evoked from cutaneous and high threshold muscle afferents makes it difficult to compare the detailed effects to α- and γ-motoneurones. Further investigations are required but at present there is no strong evidence to disprove the hypothesis of an α-γ-linkage of reflex effects from these afferents. The finding that short-latency reflex effects can be evoked both in dynamic and static γ-motoneurones raises the question of a linkage between α-motoneurones and both types of γ-motoneurones. Effective reflex activation of the two types of γ-motoneurones occurred under different experimental conditions. It is not known if the effects to static and dynamic γ-motoneurones are transmitted via different reflex pathways or whether the differences in reflex transmission mainly depends on a differential excitability in the two types of cells due to other factors (cf. below and paper III).

SUPRASPINAL CONTROL VIA TWO FAST DESCENDING SYSTEMS

The presence of monosynaptic connexions to lumbosacral α-motoneurones from descending fibres were demonstrated by Eide, Lundberg and Voorhoeve (1961). These fibres have subsequently been found to be largely derived from two supraspinal regions. One is the Deiters' nucleus that gives supraspinal effects to knee and ankle extensors (Lund and Pompeiano 1968, Grillner, Hongo and Lund 1969) and the other can be activated within a very limited region of the ipsilateral medial longitudinal fascicle (MLF) (Grillner and Lund 1968) by fibres that were postulated to originate in the lower pontine reticular formation. This descending system gives monosynaptic effects to knee and ankle flexors as well as hip and some toe extensors. In the analysis of the origin of these effects to α-motoneurones chronic lesion experiments were employed, as well as a correlation of the threshold for evoking the monosynaptic effects with the location of the Deiters' nucleus and MLF as indicated by the antidromic field potential evoked on stimulation of the lower thoracic ventrolateral funicle. The location of the stimulation electrode was always checked histologically.

In paper I it is shown with intracellular technique that lumbosacral γ-motoneurones also receive monosynaptic excitation from descending fibres activated at the lower thoracic level and coursing in the ipsilateral ventral quadrant. EPSPs have been considered as monosynaptic when occurring with a latency of 0.4—0.9 msec, from the peak of the positivity in the descending volley recorded at cord dorsum of the segment, to the onset of the EPSP. This peak can be assumed to signal the arrival of activity in the fastest descending fibres (Lund and Pompeiano 1968, Grillner and Lund 1968, Grillner, Hongo and Lund 1969). The "segmental latency" includes the conduction time in the arborizing terminals of the descending fibres and the actual synaptic delay.

To analyze the supraspinal origin of these effects stimulating electrodes were located in the Deiters' nucleus and the MLF respectively with the same criteria as used in the studies on α-motoneurones (cf. above). Since only the ipsilateral ventral quadrant was left intact the risk for coactivation of other descending systems is decreased; furthermore since only monosynaptic effects evoked by fast conducting fibres (100 m/sec) were studied, the risk for trans-synaptic activation of other descending systems can be neglected. Monosynaptic EPSPs could be evoked with low threshold in lumbosacral γ-motoneurones from either of the two regions. γ-motoneurones belonging to a given motor nucleus received monosynaptic excitation with low threshold from the same region as the α-motoneurones did (paper I). In each experiment also α-motoneurones were recorded and they could be monosynaptically excited from one of the two regions with the same low threshold. Since only 13 γ-motoneurones (2 not included in paper I) with descending monosynaptic effects have been studied, great caution should be applied in interpreting these results. However, they do allow the suggestion that the two descending supraspinal systems exert parallel effects on α- and γ-motoneurones of the same motor nuclei.

Since not all γ-motoneurones received the descending monosynaptic EPSP the question was raised whether the monosynaptic control was exerted only on one type of γ-motoneurone. To test this hypothesis the γ-efferents studied in paper III and V were also tested for descending effects (IV and V) by stimulation of the ipsilateral ventrolateral funicle. These γ-efferents could be classified as static or dynamic (though less certainly to extensors, see below), and indeed monosynaptic effects were revealed in static but never in dynamic γ-motonerones. This does not necessarily imply that there is no monosynaptic effects in dynamic cells, but if so, this effect was not strong enough to discharge the cells although they were tested against a high level of background activity. Since the size of the descending monosynaptic EPSP evoked from supraspinal regions in paper I was of similar amplitude to the one obtained on stimulation of the descending fibres at lower thoracic level, the results indicate that the descending EPSPs evoked in the γ-motoneurones investigated are largely of supraspinal origin and that strong effects are exerted on static γ-motoneurones.

It is of some interest that driving of primary endings can be elicited from the "fast descending system" of Granit and Holmgren (1955). Driving seems to be an exclusive action of static γ-motoneurones (Crowe and Matthews 1964 b, Appelberg, Bessou and Laporte 1966). Although this system is activated from the contralateral tegmentum its fibres descend in the ventral quadrant of the ipsilateral side, hence this system could be identical with the systems investigated in the present study.

In Fig. 1 the descending effects to motoneurones acting at the knee joint are summarized, demonstrating the parallel effects on α- and γ-moto-

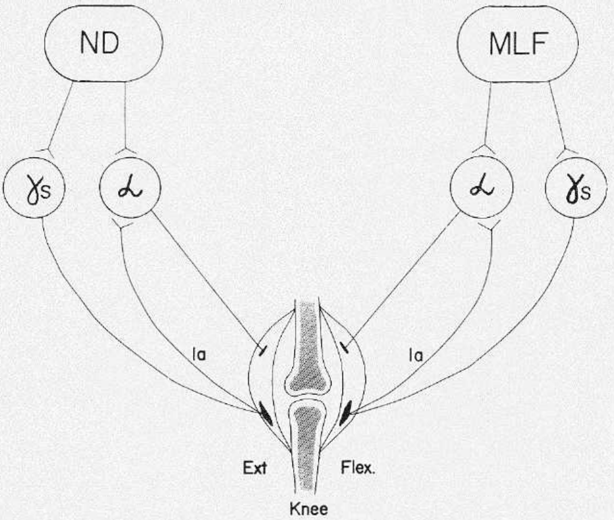

Fig. 1. Schematic representation of descending monosynaptic effects via fast conducting fibres from the Deiters' nucleus (ND) and the medial longitudinal fascicle (MLF) on to α- and static γ-motoneurones to flexors and extensors acting at the knee joint. All indicated synapses are excitatory.

neurones from the two descending systems acting on the antagonist muscle. If the assumption is made that the cells/fibres stimulated in either the Deiters' nucleus or in the MLF with uniform high conduction velocity are a functional entity, the results indicate that there is a linkage in descending effects on α- and static γ-motoneurones of the same motor nucleus. During a constant static fusimotor activity the primary endings are not unloaded. During muscular shortening, e. g. contraction (Lennerstrand 1968 a, b), the unloading mechanisms provide a negative feedback, which counteracts any shortening. Thus to obtain an efficient contraction a coactivation of α-motoneurones and static γ-motoneurones seems purposeful.

Since these two descending systems are reciprocally organized at least in their effects to the muscles of the knee and the ankle it is possible that they are functionally related to each other (Grillner, Hongo and Lund 1968). They are both large fibre systems and at least the vestibulospinal system is closely linked to the cerebellum. These descending systems would be well suited to subserve rapid motor adjustments; the coactivation of α- and static γ-motoneurones then being particulary meaningful.

THE "NORADRENERGIC RETICULOSPINAL SYSTEM"

Descending fibres in the spinal cord containing large amounts of noradrenaline were described by Carlsson, Falck, Fuxe and Hillarp (1964); subsequently Dahlström and Fuxe (1965) demonstrated that these fibres originate from cell bodies located in the reticular formation of the lower brain stem. No neurones with their cell bodies located in the spinal cord were found to contain noradrenaline (Carlsson et al. 1964). The injection of DOPA, i.e. a precursor of noradrenaline, has been postulated to cause an increased synthesis and liberation of noradrenaline from descending noradrenergic fibres (Andén, Jukes, Lundberg and Vyklicky 1966 a, Andén, Jukes and Lundberg 1966 b). The evidence relating the injection of DOPA to the formation and liberation of noradrenaline has been summarized in paper III. *On the basis of this postulate the effects of the descending noradrenergic system can be studied in the acute spinal cat after an intravenous injection of DOPA.*

The injection of DOPA causes a profound change in reflex transmission in the spinal cord. Thus the short-latency effects evoked from cutaneous, high threshold joint, group II and III muscular afferents (i.e. FRA) to α-motoneurones and ascending neurones are depressed (Andén et al. 1966 a), but, on the other hand, late reflex effects evoked with long central delay occur in α-motoneurones and in the terminals of Ia afferents (Andén, Jukes, Lundberg and Vyklicky 1966 c, Jankowska, Jukes, Lund and Lundberg 1967).

A. The resting discharge and the identification of static and dynamic γ-motoneurones

In paper III it was found that the single efferents to flexors could be subdivided in two groups, one with a resting discharge that was decreased after DOPA, the other with no resting discharge initially, but which acquired a spontaneous activity after DOPA. Identification of these two groups of γ-motoneurones in terms of dynamic and static can be made by a comparison with results obtained with indirect methods. Thus, Alnaes, Jansen and Rudjord (1965) found evidence for a resting discharge only in dynamic γ-efferents in the spinal cat and Grillner, Hongo and Lundberg (1967) showed that static γ-motoneurones are accelerated after DOPA. For the identification it was also necessary to know whether the activity in dynamic γ-motoneurones changed after DOPA. In paper II the response of primary endings to linear stretch at different velocities was studied; the dynamic sensitivity, the peak and the mean frequencies during stretch were decreased to lower values after DOPA, although there was evidence for an increased static fusimotor bias. The possibility of a tonic slow α-activity was excluded, since there was no EMG activity in the tenuissimus muscle before DOPA. These findings can only be interpreted as a decreased dynamic γ-motor drive to the spindles after DOPA. This evidence is further supported by the previously discussed reflex effect evoked from repetitive nerve stimulation (page 11). At low frequencies neurones classified as both static and dynamic γ-motoneurones could be activated; at a stimulation frequency of 40 pps only neurones classified as dynamic were activated, which was the frequency employed by Alnaes, Jansen and Rudjord (1965) when they found reflex activation of only dynamic γ-motoneurones. Since the type of γ-motoneurones obtained during the isolation procedure is largely random it is of relevance that 7 γ-motoneurones could be classified as dynamic and 15 as static, corresponding approximately to the ratio of the numbers of dynamic and static γ-efferents, which is 1 to 3 (Bessou and Laporte 1966).

Hence the two types of γ-efferents to flexors (paper III) could be identified in terms of dynamic and static. Accordingly the noradrenergic descending system exerts a reciprocal control of dynamic and static γ-motoneurones to flexors.

γ-efferents to extensors (gastrocnemius) were almost invariably accelerated after DOPA (paper V). 4 out of 15 had a resting discharge before DOPA. The identification of these neurones in terms of dynamic and static is more difficult than was the case with flexor cells. On the basis of a comparison with the results of Alnaes, Jansen and Rudjord (1965) the tentative suggestion was made that the four neurones with a resting discharge before DOPA were of the dynamic type and those without a resting discharge were of the static type. This was again supported by the effects of repetitive nerve stimulation with the same findings as discussed above for flexors. Since all γ-efferents (except one) were accelerated after DOPA, it can be inferred, even if the above tentative identification should prove to be wrong, that both dynamic and static γ-efferents to extensors are accelerated after DOPA.

The results thus indicate that the descending noradrenergic system creates a situation with a static fusimotor activity to flexors and a dynamic and a static activity to extensors. The functional implications of this will be discussed below (cf. page 27).

The generation of the resting activity in the spinal cat is largely dependent on the activity in the dorsal roots (Hunt 1951), although some activity may persist after secion of the dorsal roots (Voorhoeve 1960, Lindsley and Eldred 1960). Also the resting activity in neurones spontaneously active after DOPA is greatly reduced after transection of the dorsal roots of the neighbouring segments (paper III, V). Thus it can be concluded that the afferent inflow in tonically discharging afferents, presumably from a large variety of receptors, maintains this activity; in this connexion it is of particular interest that the receptive fields from which the γ-motoneurones can be influenced is very large (paper V). It is likely that the resting activity in γ-motoneurones spontaneously discharging before DOPA is maintained through the short-latency reflex paths to γ-motoneurones. A more complex situation exists after DOPA when both short-latency pathways and the pathways mediating the late discharge are open. A more detailed discussion of different factors of importance is given in paper III.

B. The effect of DOPA on the reflex discharge evoked through short latency reflex paths in static and dynamic γ-motoneurones

The short-latency transmission from the flexor reflex afferents (FRA) to certain ascending pathways and to α-motoneurones is depressed after DOPA, very likely due to a depression at an interneuronal level (Andén et al. 1966 a).

The reflex discharge evoked in γ-motoneurones from the FRA has been compared before and after DOPA in flexor (paper III) and extensor γ-motoneurones (paper V). In flexor γ-motoneurones a rather consistent pattern was found. The reflex discharge in dynamic γ-motoneurones was smaller after DOPA; the resting discharge, however, also ceased. Static γ-motoneurones on the other hand are more effectively activated after DOPA, though a resting discharge appears. In extensor γ-motoneurones mixed excitatory and inhibitory effects were often elicited; furthermore the excitability in all γ-motoneurones increased after DOPA as reflected by the increased resting discharge. Whether this is due to a facilitation of short latency excitatory pathways or to other factors is not known.

Hence it is not possible to conclude whether this change of reflex effects reflects only a modified excitability of the γ-motoneurones or if it is due to influences on the short-latency interneuronal pathway.

C. The late reflex discharge

Neuronal systems for alternate activation of the limb muscles do exist in spinal cord, since in the chronic spinal cat stepping movements can occur for long periods (Sherrington 1910). Graham Brown (1911, 1914) showed that it is essentially due to an intraspinal process. In an unanaesthetized (decerebrate) acute spinal cat with its hindlimbs intact, stepping movements can be induced by a variety of adequate stimuli after the injection of DOPA (unpublished observation). The late and longlasting reflex discharge that can be evoked from ipsilateral nerves in flexor motoneurones and from contralateral nerves in extensor motoneurones after an injection of DOPA, can give rise to alternate activation of flexors and extensors similar to "spinal stepping" (Jankowska et al. 1967, cf. paper V, Fig 1). It has been suggested that stepping can be evoked through the interneuronal network responsible for these reflex discharges not only by reflex effects from spinal afferents but also by effects in descending pathways and probably also from autochtonus interneuronal activity (Jankowska et al. 1967).

α-motoneurones and also static and dynamic γ-motoneurones participate in the late reflex discharges to extensors and flexors (paper III, V). In most instances there was a slowing of the resting discharge in extensor γ-motoneurones during the reflex discharge in flexors, which would be meaningful since it decreases the reciprocal Ia inhibition evoked in antagonists (paper V).

The results thus infer that the activation of descending noradrenergic fibres reveals a neuronal system for alternate activation of flexors and extensors. It is of considerable interest that both dynamic and static γ-motoneurones are activated with α-motoneurones in the late discharge. The functional implications of linkage will be further discussed below.

D. The stretch reflex

In the decerebrate preparation a tonic stretch reflex occurs in extensor muscles, but not in the acute spinal preparation (Liddell and Sherrington 1924). After an injection of DOPA, however, a tonic stretch reflex does occur in the soleus muscle (paper V) as judged from an increased EMG activity together with an increase of tension on extension of the muscle. Also in flexor muscles a stretch reflex occurs (unpublished observation). This effect occurs in parallel with an appearance of a resting discharge in static γ-motoneurones (see above). Since after DOPA no apparent change in excitability occurs in α-motoneurones in the spinal curarized preparation used by Andén et al. (1966 a) with most ipsilateral and several contralateral nerves cut, it is tempting to relate this tonic myotatic reflex to the occurrence of a static fusimotor activity. In the decerebrate preparation there is a spontaneous activity in static γ-motoneurones (Jansen and Matthews 1962 a, b, Jansen 1966) but in the spinal preparation only dynamic γ-motoneurones appear to be spontaneously active (Alnaes, Jansen and Rudjord 1965, cf. paper II). The decerebrate preparation has been described as "a caricature of standing" (Creed et al. 1932); in the spinal cat after DOPA with its hindlimbs pendent both flexors and extensors are at rest with no sign of EMG activity (unpublished observation). One important difference between the decerebrate preparation and the "DOPA preparation" is that in the former, practically no resting activity occurs in γ-motoneurones to flexors (Jansen and Rudjord 1965) whereas the "DOPA preparation" has a resting discharge in static γ-motoneurones to both flexors and extensors (paper III, V), which gives rise to a discharge in afferents from muscle spindles in both types of muscles; the reciprocal Ia inhibitory effects exerted in both directions between flexors and extensors might provide an explanation for the lack of tonus in the "DOPA preparation" at rest (cf. above C).

GENERAL DISCUSSION OF THE PROPERTIES OF THE γ-MOTOR SYSTEM WITH PARTICULAR REFERENCE TO THE SYSTEMS INVESTIGATED IN PAPERS I-V

Papers I—V are mainly concerned with the central control of γ-motoneurones. In an effort to understand the possible role of the γ-loop during posture and locomotion, some of its properties will be considered. The muscle spindle will be treated as a black box; some characteristics of its input-output relations will be discussed and also some quantitative aspects of data relevant to the transfer function of the different elements in the stretch reflex loop. Very little attention will be paid to the inhibitory effects evoked from Ia afferents in antagonist motor nuclei (Lloyd 1946), although it should be emphasized that these effects presumably are of great functional significance in motor control.

A. Properties of the stretch reflex loop

The different input variables are the frequency of impulses in fusimotor fibres and the muscle length and its derivative, the velocity of length change. It has been proposed (Schäfer 1967, Grüsser and Thiele 1968) and subsequently denied (Lennerstrand 1968 b) that the spindle is also sensitive to acceleration. This possibility will not be discussed below. The outputs of the spindle are the primary and the secondary endings. The loop from the primary ending will mainly be considered, i.e. primary ending — monosynaptic excitation of certain α-motoneurones leading to a contraction and development of tension and eventual shortening of the muscle.

The transfer functions* between both static and dynamic γ-motoneurones and the primary endings are linear, as they are from static γ-motoneurones to secondary endings within the frequency range used ($^1/_4$—12 Hz) (Andersson, Lennerstrand and Thodén 1968). With length input there is a linear transfer function with amplitudes less than 100 μ (Poppele and

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* A linear transfer function is here defined as one in which a given input (sinusoidal) at a certain frequency gives a response linearly related to the amplitude of the input and always having the same phase shift at a given frequency.

Terzuolo 1968, Matthews and Stein 1968). Poppele and Terzuolo (1968) have extended their analysis to the synaptic effect on the α-motoneurone (cf. also Redman Lampard and Annal 1968) and the development of tension induced in the muscle under a given γ-bias in an extensor muscle of the decerebrate cat. There is, at stretches below 100 μ, a linear transfer function for sinusoidal stretch between the length change and the induced change in tension. In the first part of the control loop there is a phase advance until the stage of the EMG activity, but in the last part, i.e. α-efferent (EMG) to tension development in the muscle there is a phase lag (Partridge 1965, Poppele and Terzuolo 1968). For these reasons the tension developed in the muscle followed the applied length changes without appreciable phase shift within the frequency range used (0.1—6.0 Hz). With applied sinusoidal stretching above 100 μ the transfer function between applied length change and tension development is not linear (cf. Lippold, Redfearn and Vuco 1958, Jansen and Rack 1966). It is of considerable interest, however, that the relation between motoneuronal activity and applied length can be linear over a wide range of length changes (Poppele and Terzuolo 1968). Since the increase in tension in the stretch reflex is not primarily due to a frequency modulation but rather to a recruitment of new motor units (Denny-Brown 1929, cf. Poppele and Terzuolo 1968), this implies that either the threshold or the synaptic input to, or the properties of different motoneurones supplying the muscle varies within quite a wide range.

It should be noted that with slow sinusoidal stretches the responses (tension developed) to each cycle are not identical if the experiment is performed on a decerebrate cat. Thus Higgins, Partridge and Glaser (1962) have shown that during the first few cycles (0.5—1.2 Hz) of large amplitude stretching (5 or 8 mm), the tension developed is phase advanced and of larger amplitude, reaching after less than 30 sec a steady state with no phase advance and smaller amplitude. These findings could be explained if the sinusoidal stretching decreased the activity in dynamic γ-motoneurones to the muscle studied. This transient response disappeared if the cerebellum was removed. It can therefore not be assumed that the γ-bias is identical during resting conditions and during sinusoidal stretching, or during vibration of the muscle tendon. Whether changes occur also directly in the α-motoneurones due to a similar mechanism is not known.

The reflex stiffness, i.e. the static gain of the stretch reflex loop of the soleus muscle in the decerebrate preparation, can vary considerably; values of 40—200 g. wt/mm have been given (Matthews 1959). When estimating the gain of the stretch reflex loop it is difficult to know how relevant results obtained on one single muscle are. One could visualize the possibility of a γ-bias only to one muscle acting at a joint, but more often probably γ-motoneurones to muscles which are synergistic at a joint are coactivated. The considerable heteronymous Ia excitation that, for instance exists from the gastrocnemii to the soleus, may be of importance for the gain of stretch reflex loop of the soleus muscle. Under a given fusimotor bias to antagonists and synergists working at one joint the lengthening of the synergists will unload the antagonists and thereby further increase the stretch reflex through a decreased reciprocal Ia inhibition. These factors all need to be taken into account when discussing the gain of the stretch reflex under physiological conditions.

Most pertinent to the discussion of the gain are the results obtained by Matthews (1959, 1966), suggesting that the tension developed in the soleus during the stretch reflex is very much higher if counted as a change of tension/impulse/sec in the primary endings of the muscle as compared to the tension/impulse/sec developed on vibration (Matthews 1967, 1969). During this stimulus the response of the primary endings can with reasonable certainty be predicted from the characteristics of the vibration (Brown, Engberg and Matthews 1967). If the developed tension was only dependent on the activity in primary endings one would have expected a very much higher tension developed during vibration. As an explanation for this finding Matthews (1969) has postulated that the secondary endings also provide autogenetic excitation, revealed during the stretching but not during vibration. This postulate seems to rest on the assumptions that the input from vibration in the contracting muscle is limited to Ia afferents and that the massive and rather synchronous Ia input caused by vibration does not modify the excitability of α-and γ-motoneurones through complex pathways involving supraspinal structures or through other mechanisms. It should also be noted that the vibratory stimulus as such causes a reduction in tension in the soleus muscle when the muscle is stimulated by distributed stimuli at physiological frequencies (Rack and Westbury 1968). Implicit in this postulate is further that the excitatory effects to motoneurones should be limited largely to synergic muscles. In the present context the secondary ending will not be considered as autogenetically excitatory to extensors although this postulate should be kept in mind (cf. also page 10). The stretch reflex loop will imply only the loop from the primary endings.

B. The functional role of the "γ-loop"

These results provide a basis for an estimate of what effects the γ-loop could exert, but they do not answer the question of what the γ-loop is actually used for. Merton (1953, cf. also Eldred, Granit and Merton 1953) in his follow up length servo hypothesis postulated that the "γ-loop" constituted an independent route for motor control. Merton (1953) clearly pointed out that the direct activation af α-motoneurones would be a disturbing factor for this kind of servo, and further that the gain of the loop needs to be high enough. Subsequent work of Granit and others has shown that in most cases α- and γ-motoneurones are coactivated although the γ-motoneurones often have lower threshold for excitation, which is why the expression α-γ-linkage was introduced (Granit 1955). The results presented on the segmental (paper I, III, V) and on the descending control provide further evidence for an α-γ-linkage as well as the results obtained during naturally elicited alternating rhythmical movements (cf. below page 27). It has also been argued that the gain of the stretch reflex loop is too low (in soleus 40—200 g. wt/mm) to allow operation of an independent follow-up-length-servo (Matthews 1967). For these reasons and since the evidence used to support Merton's (1953) hypothesis merely shows that the excitability of the α-motoneurones is dependent on activity in muscle spindle afferents (cf. Hunt and Perl 1960 and Matthews 1967), the γ-loop will in the present context not be considered as an independent route for motor excitation. However, the "γ-loop" does have servo properties (cf. Matthews 1964); the primary endings are in fact accelerated instead of decelerated during a "naturally" elicited muscular contraction (cf. below), although α- and γ-motoneurones are coactivated.

It is presumably of importance when considering the function of the "γ-loop" to differentiate between posture and locomotion. In standing there is possibly a rather stable discharge in α- and γ-motoneurones. Under these conditions the muscle spindle with its afferent supply acts to counteract any change in muscle length, i.e. as a negative feedback. These negative feedback properties can be changed considerably by the γ-motor supply, and it has to be divided into a static and a dynamic component. A primary ending extended to a given length and with a resting discharge has

1) under no γ-bias a resting discharge with high dynamic sensitivity to muscle shortening (a decreased discharge, i.e. unloading), and a certain dynamic sensitivity to lengthening (increased discharge) (B. H. C. Matthews 1933);

2) during dynamic fusimotor drive there is, compared to 1), an increased dynamic sensitivity to muscle lengthening but a decreased dynamic sensitivity to muscle shortening. There is still, however, an abrubtly decreased resting discharge on shortening (Crowe and Matthews 1964 a, b);

3) during static fusimotor drive the dynamic sensitivity to both shortening and lengthening is reduced compared to 1) and 2) and the signal will be linearly related to muscle length (Crowe and Matthews 1964 a, b);

4) during a concomitant static and dynamic fusimotor drive there is a high dynamic sensitivity to muscle lengthening but not to shortening when the discharge is proportional to length (Lennerstrand 1968 a, b).

The static fusimotor drive will set the discharge rate of the primary endings (Matthews 1962, Crowe and Matthews 1964 a) and in addition presumably also increase their static sensitivity, i.e. the increased discharge on extension in imp/sec/mm (Jansen and Matthews 1962 a, Brown, Lawrence and Matthews 1969).

1. *During posture*

If during standing there is a dynamic and a static fusimotor bias (as in extensors of the decerebrate cat) a sudden increase in load leading to lengthening will be effectively counteracted by the high dynamic sensitivity. If the static loop gain is high enough the muscle will remain at approximately the same length; if not, supraspinal structures would, during the period in which the high dynamic sensitivity is acting, have time to readjust the excitability of the motoneurones. In this connexion the very high sensitivity of the primary ending for changes in muscle length below 100 or 200 μ should be considered (decerebrate cat, Terzuolo and Poppele 1968, Matthews and Stein 1968). It is then tenfold higher than during larger amplitudes of stretch. In other words, the gain of the stretch reflex loop is much higher in this range and would detect and counteract even very small length changes. Thus, if α- and γ-motoneurones are coactivated and have brought a muscle to a certain length, the stretch reflex will act as an efficient circuit for maintaining the length (cf. Matthews and Stein 1968). It is of interest to make a comparison with the frog that has a slow and a fast (twitch) extrafusal motor system. The slow motor system that presumably is involved in postural activities increases the dynamic sensitivity of the spindle but the fast twitch system increases the static discharge of the spindles (Matthews and Westbury 1965). It should perhaps be noted that the viscoelastic proporties of the muscle itself, which differs considerably in the active and passive states, also counteracts lengthening.

2. *During movement*

The muscle spindle presumably has a different role in phasic movement. The primary endings are accelerated during naturally elicited movements such as the respiratory movements (Critchlow and Euler 1963), the locomotion that can be induced in the mesencephalic cat (Severin, Orlovskii and Shik 1967) and the reflexly initiated contraction of the jaw muscles (Taylor and Davey 1968); efferent recordings have shown that both α- and γ-efferents participate (Eklund, Euler and Rutkowski 1964, Shik, Orlovskii and Severin 1966). Euler and Peretti (1966) have found that dynamic and static γ-motoneurones appear to be coactivated in the respiratory movements. The alternate stepping movements might be the corollary of activity in the neuronal system mediating the late reflex discharges that can be evoked after DOPA (cf. page 20, Jankowska et al. 1967). α- and γ-motoneurones of both types participate in these reflex discharges (paper III, V). How does the fusimotor activity influence movements? The advantage of dynamic fusimotor activity is the same as during standing. However, a muscle spindle with dynamic sensitivity to muscles shortening (decreased discharge) would counteract the contraction. A coactivation of α- and static γ-motoneurones removes this effect, since the primary endings are not unloaded; indeed it has been shown that an acceleration of static γ-motoneurones during a shortening (in contrast to dynamic γ-motoneurones) is able to cause an increased discharge rate in the primary endings (Lennerstrand and Thodén 1968). This would not only compensate for the unloading but also add excitation to the α-motoneurones through the γ-loop, the amount of excitation being dependent on the actual length of the muscle. Thus it can be concluded from the above findings that a static γ-α-linkage indeed occurs under natural conditions and that the activation of static γ-motoneurones gives servo properties to the γ-loop.

3. *What is the functional role of the resting discharge in γ-motoneurones?*

In the spinal state there is a resting discharge mainly in dynamic γ-motoneurones (Alnaes, Jansen and Rudjord 1965, paper II); the preparation is then counteracting any changes of length with its dynamic sensitivity to lengthening and shortening, the overall effect being a general damping of movement in the system (cf. Alnaes, Jansen and Rudjord 1965). After DOPA, i.e. under influence from descending noradrenergic fibres, the resting discharge of γ-motoneurones changes; flexor γ-motoneurones of the static type acquire a resting discharge but the dynamic are depressed; to extensors on the other hand the resting discharge of both types of

γ-motoneurones is increased. The functional significance of this change of the resting discharge is obscure. However, if the very speculative assumptions are made that 1) the descending noradrenergic system activated by DOPA is one functional entity and not several separate descending systems provided with the same transmitter and 2) that the injection of DOPA reveals the neuronal pools employed during stepping (Jankowska et al. 1967, see above), it is relevant to ask if the change of γ-bias to flexors and extensors induced by the noradrenergic system would be purposeful for the act of stepping, i. e. if the adjustment of γ-bias can be looked upon as a preparatory state for locomotion.

During stepping, rapid forceful alternate contractions of flexors and extensors are required. The damping properties, i.e. the dynamic sensitivity to lengthening and shortening is probably not particularly important for flexors, since their function in locomotion is to rapidly flex and bring forward the leg and not to counteract the lengthening. With a γ-bias of only the static type, the spindle has its lowest dynamic sensitivity to both lengthening and shortening. During the late discharge there is a concomitant activation of all three types of motoneurones, including dynamic γ-motoneurones, but since during contraction the discharge of the primary ending is entirely influenced by the discharge in static γ-efferents this does not essentially change the condition. The situation in the extensors during locomotion differs considerably from that of flexors since then the contraction will lead not only to an extension of the leg resulting in the propulsive force for the body but will also support the body, i.e. being antigravitatory. The resting discharge in static and dynamic γ-motoneurones thus provides a situation with no dynamic sensitivity during the contraction, but an eventual lengthening would be counteracted by the dynamic sensitivity to lengthening provided by the discharge in dynamic γ-motoneurones.

Hence it seems as if an activation of the descending noradrenergic system changes the resting discharge in static and dynamic γ-motoneurones towards a γ-bias that would give an appropriate background discharge during locomotion on which the phasic activation of α- and γ-motoneurones can be superimposed.

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