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# ROLE OF THE LOCUS COERULEUS IN THE STATIC AND DYNAMIC CONTROL OF POSTURE

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## INTRODUCTION

In 1953, Aserinsky and Kleitman (2) described in humans a new phase of sleep, characterized by the occurrence of rapid and binocularly symmetrical eye movements, apparently associated with dreaming, and by a low amplitude electroencephalogram (EEG). This phase of sleep, now called REM sleep, occurs also in several animal species, including the cat, where isolated ocular jerks intermingled with bursts of rapid eye movements appear during episodes characterized by desynchronization of the EEG and suppression of posture (cf. 38).

Our contribution to the understanding of the neurophysiological mechanisms responsible for this phase of sleep started in the early sixties, when we differentiated the mechanisms responsible for bursts of REM and all the *phasic* somatic (muscle twitches) and sensory events related to them, on one hand, from those responsible for the *tonic* events characterized by the EEG desynchronization and postural atonia (56, 57). By using several lines of evidence we demonstrated that the suppression of postural activity which occurs during this phase of sleep was not due to a reduced discharge of lateral vestibular nucleus (LVN) neurons, leading to disfacilitation of extensor motoneurons (7), but rather to inhibition of these motoneurons (56; cf. also 27, 47). Since then, experiments were performed in several laboratories aimed at investigating the role that the dorsolateral pontine tegmentum exerts in suppressing the postural activity during REM sleep (cf. 33, 59 for ref.). This region includes the locus coeruleus complex, made by the locus coeruleus (LC) and subcoeruleus (SC), which facilitate posture by utilizing in part a direct coeruleospinal (CS) projection, in part an indirect projection passing through the dorsal pontine reticular formation (pRF) and the related medullary reticulospinal (mRS) system (cf. 6 for ref.).

Experiments performed in our laboratory during the last decades have shown that while the LVN exerts an executive role in the control of posture, the dorsolateral pontine tegmentum, characterized by the LC complex and the closely related pRF neurons, exerts a permissive role. In particular, observations reported in the following sections indicate that both the LVN as well as the neuromodulatory

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structures located in the dorsolateral pontine tegmentum play a prominent role not only in the static but also in the dynamic postural adjustments induced by vestibular stimulation.

## STATIC CONTROL OF POSTURE

A. *Role of the LVN.* - Classical observations have shown that the postural activity, which increases after decerebration, is suppressed either after transection of the ventrolateral column of the spinal cord or after limb deafferentation (78, 79). The postural atonia which occurs after spinal cord section depends on interruption of supraspinal descending systems originating from vestibular nuclei and the lateral part of the medullary reticular formation (42), which exert a facilitatory influence on posture. On the other hand, the suppression of the postural activity after limb deafferentation has been attributed to the fact that the supraspinal descending systems would not activate the extensor $\alpha$-motoneurons directly, but rather indirectly through the $\gamma$-loop made by fusimotor neurons, muscle spindle receptors and group Ia primary afferents (28). The hypothesis that the decerebrate rigidity is essentially a $\gamma$-rigidity is supported by the fact that in the decerebrate cat there is a tonic discharge of $\gamma$-motoneurons innervating the extensor muscles (28). The following experiments, however, indicate that the decerebrate rigidity is not a pure $\gamma$-rigidity, but rather results from a co-activation of the $\alpha$-$\gamma$ systems.

It is known that the LVN, which contains large, medium-sized and small neurons (63), gives rise to a vestibulospinal (VS) projection which descends ipsilaterally to the whole segments of the spinal cord. This pathway shows a somatotopically organized pattern, with the rostroventral part of the nucleus projecting to the cervical and thoracic segments of the spinal cord, while the dorsocaudal part projects to the lumbosacral segments (63). By recording in decerebrate cats the intracellular activity of spinal motoneurons, we have shown that stimulation of the LVN produces monosynaptic and polysynaptic EPSPs in hindlimb extensor motoneurons (41). These findings were confirmed and extended by several investigators, who also recorded monosynaptic and/or polysynaptic EPSPs in axial (neck), and forelimb extensor motoneurons (cf. 30, 58, 88). The same structure also produced disynaptic IPSPs in ipsilateral flexor motoneurons (41), an effect which was attributed to monosynaptic activation of interneurons mediating the antagonistic Ia inhibition from limb extensor muscles to flexor motoneurons (cf. 30).

After the discovery that the LVN exerts a direct excitatory influence on ipsilateral limb extensor motoneurons, the problem of the possible link between this structure and the fusimotor system has been investigated. In particular, Carli *et al.* (10, 11) and Pompeiano *et al.* (64) discovered that repetitive electrical stimulation of the LVN, performed in anesthetized or in decerebrate cats, increased the discharge of spindle afferents originating from ipsilateral hindlimb extensor muscles, due to activation of the corresponding fusimotor neurons. This effect paralleled the development of contraction of the extensor muscles, due to activation of skeletomotor neurons. Moreover, both spindle activation and extrafusal contraction occurred at

the same stimulus intensity and increased with increasing frequency of LVN stimulation. The finding that both primary and secondary endings of muscle spindles were accelerated during stimulation of LVN indicated that static γ-motoneurons were influenced by this structure. Moreover, indirect evidence suggested that the VS pathway affected the fusimotor neurons both directly as well as through spinal interneurons. In line with these findings, Grillner (29) and Grillner *et al.* (31) observed that stimulation of LVN produced both monosynaptic and polysynaptic EPSPs in extensor γ-motoneurons, as shown for extensor α-motoneurons. These effects occurred in static, but not in dynamic γ-motoneurons. Moreover, the excitation of extensor γ- was associated with inhibition of flexor γ-motoneurons (39). All these findings indicate that the decerebrate rigidity results from co-activation of the α-γ systems. In particular, due to this α-γ linkage, the tonic contraction of the extensor muscles following LVN stimulation was attributed to direct activation not only of tonic α-motoneurons, but also of static γ-motoneurons, which prevented the decrease in spindle discharge from occurring during contraction of the extrafusal muscle fibers (12). The same stimulus could also potentiate directly and through the γ-loop the activity of the interneurons mediating the antagonistic Ia inhibition to flexor motoneurons (cf. 30).

The role that different size LVN neurons, which contribute to the VS projection, exerts in the static control of posture has been investigated in decerebrate cats in which the resting discharge of spontaneously active VS neurons projecting to the lumbosacral segments of the spinal cord (lVS neurons) has been related to the cell size inferred on the basis of the conduction velocity of their axons (cf. 61). In normal decerebrate cats a slight negative correlation was found between the resting discharge of all the recorded lVS neurons and the conduction velocity of the corresponding axons, so that the faster the conduction velocity, the lower was the unit discharge rate at rest (paired rank, $P < 0.01$) (70). This relation was lost after unilateral acute vestibular neurectomy, due to a decrease in resting discharge rate of the slow units, but was re-established after chronic vestibular neurectomy (73). These findings indicate that the small-size VS neurons, having a slow conduction velocity, are particularly sensitive to the tonic excitatory input originating from the ipsilateral labyrinth in the animal at rest, thus contributing in the decerebrate cat to the tonic discharge of both the small tonic α-motoneurons and the static γ-motoneurons innervating the extensor muscles. The small-size lVS neurons also contribute to the development and compensation of the static postural deficits following ipsilateral vestibular deafferentation. It is of interest, however, that both small-size as well as large-size lVS neurons intervene in the dynamic control of posture during sinusoidal stimulation of labyrinth receptors (see Section 2, A).

The lVS neurons receive not only a direct excitatory input from the ipsilateral labyrinth, but also a monosynaptic inhibitory influence from the paramedian zone B of the cerebellar anterior vermis (cf. 36), via a direct cerebellar cortico-vestibular projection (17, 84). Moreover, ablation in the decerebrate cat of the cerebellar vermis and the underlying fastigial nuclei leads to a prominent increase in postural activity which persists after limb deafferentation (thus being called α-rigidity, 55).

In these instances, the negative correlation between the resting discharge of all the recorded lVS neurons and the conduction velocity of the corresponding axons greatly increased (paired rank, $P < 0.001$) (9). This finding was due to a selective increase in the discharge rate of the small-size lVS neurons, while that of the large-size neurons was only slightly affected. It appears, therefore, that the cerebellum exerts a prominent inhibitory influence on the small-size lVS neurons. The increased discharge of these neurons after cerebellectomy would increase the postural activity due to a recruitment of larger size $\alpha$-motoneurons. However, since these large units are particularly effective in driving the Renshaw (R)-cells (cf. 60), the resulting increase in recurrent inhibition would attenuate or suppress the activity of small tonic motoneurons, particularly of the static $\gamma$-motoneurons (cf. 60), thus accounting for the $\gamma$-paralysis which occurs after cerebellectomy (28).

B. *Role of the dorsolateral pontine tegmentum.* - The LC complex is made by noradrenergic and norepinephrine (NE)-sensitive neurons, due to the existence of the self-inhibitory synapses acting on $\alpha_2$-adrenoceptors through mechanisms of recurrent and/or lateral inhibition (cf. 6). This structure gives rise to both direct and indirect projections to the spinal cord.

The direct CS projection forms a plexus of thin fibers terminating in part at least in the ventral horn, where they surround large and small-size cells, presumably $\alpha$- and $\gamma$-motoneurons, as well as interneurons (16, 18; cf. 6 for ref.). This pathway may exert a facilitatory influence on spinal reflexes by activating both skeletomotor (cf. 5) and fusimotor neurons (cf. 16). These effects were mimicked by NE, which did not act on spinal motoneurons as a neurotransmitter, but rather as a neuromodulator. In fact, microiontophoretic application of NE increased the extracellularly recorded firing of rat spinal motoneurons, and also produced in rats and cats a slowly developing small-amplitude depolarization in intracellularly recorded units. This neuromodulatory effect outlasted the ejection period and was associated with an increase in the glutamate-evoked motoneuronal firing (86, 87; cf. 85 for ref.). In addition to this direct excitatory influence on spinal $\alpha$-motoneurons, the CS system depressed the activity of inhibitory Renshaw (R)-cells, thus leading to disinhibition of small-size tonic $\alpha$-motoneurons as well as of static $\gamma$-motoneurons (24, 25). In particular, the inhibitory influence of the CS system on R-cells emerged from experiments performed in decerebrate cats, in which monosynaptic reflexes, recorded from a split bundle of the $L_7$ ventral root following stimulation of the gastrocnemius-soleus (GS) or common peroneal (CP) nerve, were conditioned with a single volley delivered to the remaining bundle of the $L_7$ ventral root at the appropriate interval (6-18 msec) to elicit a prominent recurrent inhibitory effect. The ventral root-induced recurrent inhibition was regularly counteracted by LC preconditioning stimuli (3-4 cathodal pulses of 0.7 msec, at 770/sec). Such a decrease in recurrent inhibition, involving both extensor (GS) and flexor (CP) motor nuclei, depended on a NE-mediated CS suppression of R-cell activity. The evidence for this is that: 1) recurrent inhibition was reduced in some cases, even in the absence of any measurable facilitation of the monosynaptic reflex attributable to a direct depolarizing influence of the CS projection on spinal motoneurons;

2) the magnitude of LC-induced disinhibition was significantly correlated with that of the ventral root-induced recurrent inhibition, i.e. the greater the recurrent inhibition, the larger the disinhibition; 3) the high frequency discharges of R-cells recorded intracellularly in response to ventral root volleys were inhibited by LC conditioning (24, 25). It appeared also that the R-cell activity was inhibited by iontophoretically applied NE (cf. 25 for ref.) (see Fig. 1).

It is of interest that the facilitatory influence of NE and adrenergic drugs on ventral horn cell activity was mediated by $\alpha_1$-adrenoceptors, as it was depressed by $\alpha_1$-antagonists (32, 81; cf. 5, 85 for ref.). On the other hand, the facilitatory effect of the noradrenergic system on spinal motor system was depressed by $\alpha_2$-

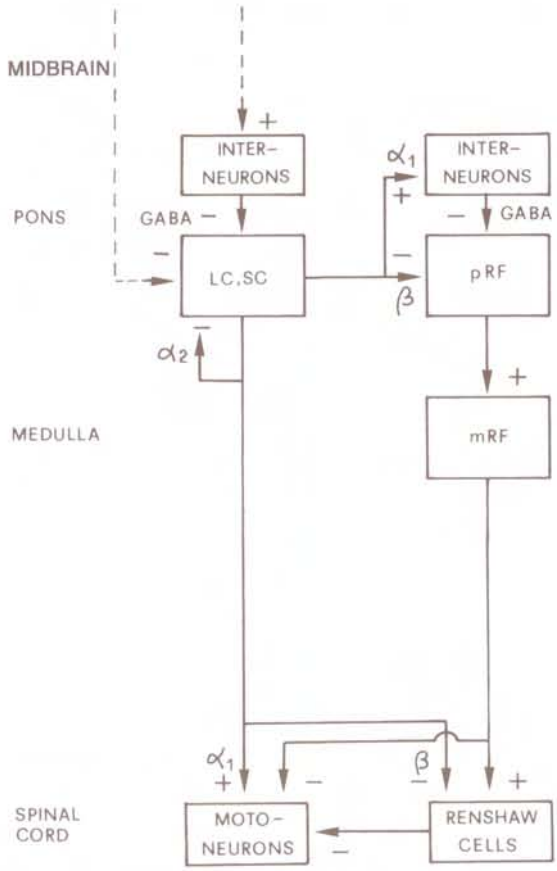


Fig. 1. - *Descending projections from the noradrenergic LC-SC nuclei to the spinal cord.*

They include a direct coeruleospinal projection, as well as an indirect projection passing through the dorsal pontine reticular formation (pRF) and the related medullary reticular formation (mRF), from which inhibitory reticulospinal systems originate. $\alpha_1$, $\alpha_2$ and $\beta$ refer to different types of adrenoceptors; + and – indicate postsynaptic excitatory and inhibitory effects on various targets. Dashed lines refer to supramesencephalic descending systems which tonically suppress the activity of the LC-SC nuclei either directly, or through activation of inhibitory interposed neurons.

agonists, which reduced the release of NE either at spinal cord level (32, 81) or more prominently at supraspinal (LC complex?) level (51). Finally, the inhibitory effect of NE on the R-cell activity was apparently mediated through β-adrenoceptors (cf. 25 for ref.).

In addition to the direct CS projection there is also an indirect projection of the LC complex to the spinal cord (see Fig. 1). This pathway is made by noradrenergic afferents, which act on presumably cholinergic and cholinosensitive neurons located in the dorsal part of the pRF by inhibiting them (6; cf. 65 for ref.). This inhibitory influence was in part at least directly mediated by β-adrenoceptors (cf. 65), in part was attributed to activation through $\alpha_1$-adrenoceptors of GABAergic inhibitory interneurons (15). On the other hand, the dorsal pRF neurons project to the inhibitory regions of the medullary reticular formation, on which they exert an excitatory influence (cf. 65 for ref.). The corresponding reticulospinal (RS) projection may in part at least inhibit spinal motoneurons by activating R-cells (cf. 60).

The LC and the SC nuclei exert a prominent facilitatory influence on the postural activity in the ipsilateral limbs by utilizing both their direct and indirect projections to the spinal cord. We have in fact shown that in decerebrate cats the postural activity was reduced or suppressed by the following unilateral procedures: 1) electrolytic lesion of the LC complex (cf. 65); 2) microinjection into this structure either of the $\alpha_2$-adrenergic agonist clonidine (cf. 65) or of $GABA_A$ and $GABA_B$ agonists, which inhibited postsynaptically the LC neurons (unpublished); 3) microinjection into the dorsal pRF either of the β-adrenergic antagonist propanolol (cf. 65) or of the $\alpha_1$-adrenergic antagonist prazosin (15), which released from direct or indirect noradrenergic inhibition the dorsal pontine reticular neurons; 4) microinjection into the pRF of the cholinergic agonists carbachol or bethanecol (a muscarinic agent), which activated the cholinoceptive pontine reticular neurons and the related medullary RS neurons (cf. 65), thus leading to postsynaptic inhibition of limb extensor motoneurons (48). Just the opposite result, i.e. an increase in postural activity in the ipsilateral limbs, occurred after local microinjection into the LC complex of one side of a muscarinic agonist, which exerted an excitatory influence on the corresponding noradrenergic neurons (80).

The conclusion of these studies, i.e. that the LC neurons as well as the related pRF neurons contributed to the decerebrate rigidity, was supported by the results of unit recording experiments showing that in decerebrate cats the postural activity was present as long as the noradrenergic LC complex neurons fired regularly, thus keeping under the inhibitory control the pRF neurons. However, as soon as the LC neurons ceased firing, as shown after systemic injection of an anticholinesterase, the discharge rate of the presumably cholinergic and cholinosensitive pRF neurons, as well as the inhibitory RS neurons increased, thus suppressing posture (34, 66, 67; cf. 59 for ref.). Similar results occurred also in intact, unanesthetized cats during the spontaneous sleep-waking cycle. In fact, the resting discharge of the LC neurons, which contributes to the postural activity during waking, decreased or disappeared during the episodes of postural atonia typical of desynchronized sleep (3; cf. 22, 33, 50 for ref.), while that of the pRF neurons and related medullary inhibitory RS neurons increased (cf. 33 for ref.). In addition to these findings there

is evidence that the LC neurons became silent during the cataplectic episodes, characterized by a loss of muscle tone, which occurred in canine narcoleptics either as a result of sudden emotionally significant stimuli or following oral administration of an $\alpha_1$-antagonist (prazosin) or i.v. injection of an anticholinesterase (physostigmine) (90). These observations lead to the conclusion that the LC activity contributes to the maintenance of muscle tone in waking, and that reduction in LC discharge plays a role in the loss of muscle tone both in cataplexy and REM sleep. It has been postulated that the reduced activity of LC neurons observed during the cataplectic episodes induced by an anticholinesterase in decerebrate cats (66, 67; cf. 59) as well as during REM sleep in intact cats (3; cf. 22, 33, 50 for ref.), is not due to disfacilitation of the LC neurons, but rather depends upon a process of active inhibition which appears to be of GABAergic origin (50).

The results of the experiments reported above are relevant in order to understand why the postural activity increases after decerebration. This finding was originally attributed to interruption of the cortico-bulbo-reticular pathway originating from the area 4s of the cerebral cortex and exerting a facilitatory influence on the inhibitory region of the medullary reticular formation (42). We have seen that the resting discharge of presumably noradrenergic LC neurons, which is very low (1-2 Hz) in the intact animal during quiet waking (cf. 22, 33, 50 for ref.), increased on the average to about 10 (68, 69) or 20 Hz (66, 67) after decerebration. We proposed that this increased discharge of the LC neurons contributed to the $\gamma$-rigidity by utilizing two mechanisms: 1) the increased activity of the noradrenergic CS neurons, which exert not only a direct excitatory influence on $\alpha$-extensor (and flexor) motoneurons (5, 85-87) but also an inhibitory influence on R-cells (24, 25), thus leading to disinhibition of both tonic $\alpha$- and static $\gamma$-extensor motoneurons (cf. 60); 2) the increased noradrenergic inhibition that LC neurons exert on the dorsal pRF neurons and the related medullary inhibitory RS neurons (see above). The conclusion of our experiments, i.e. that the $\gamma$-rigidity depended upon an increased activity of the descending noradrenergic system, is supported by pharmacological studies showing that the postural rigidity, which occurred in cats or rats after intercollicular decerebration, was greatly reduced by administration of an $\alpha_1$-antagonist (23, 46, 53) or by i. v. administration (49) or fourth ventricular injections of $\alpha_2$-agonists (51). The low sensitivity of the anemic decerebrate rigidity – originally described by Pollock and Davis (54) – to $\alpha_1$-antagonists and $\alpha_2$-agonists (52, 82) can be attributed to the fact that in contrast to the $\gamma$-rigidity which occurred after intercollicular decerebration (28), anemic decerebration functionally inactivates not only the forebrain structures but also the cerebellar anterior vermis, which gave rise to $\alpha$-rigidity (55) leading to a $\gamma$-paralysis (see end of Section 1, A).

Further experiments are required to identify the supramesencephalic descending pathway, which exerts a tonic inhibitory influence on the noradrenergic LC neurons. The increased discharge of the LC neurons which occurs after decerebration could be due to interruption of a direct GABAergic inhibitory projection from the reticular part of substantia nigra to the noradrenergic neurons of the dorsal pontine tegmentum (77). Alternatively, the brainstem transection could interrupt descending pathways which act on the LC complex through GABAergic inhibitory neurons

located either in the dorsal pontine tegmentum close to the LC neurons (37) or in other structures such as the prepositus hypoglossal nucleus (4, 20).

The cascade of the inhibitory systems involved in the LC control of postural activity is schematically illustrated in Fig. 1. For sake of simplicity this scheme does not include the possible two-way interaction between the medulla and the pons which has been hypothesized to play a role in mediating the suppression of extensor muscle tone induced by medullary stimulation (40).

A final comment concerns the identification of the source of origin of the resting discharge which tonically affects the LC neurons after decerebration. In 1976 we discovered that in decerebrate cats the spontaneous discharge of the LC complex neurons depended and could actually be modified by static changes of head position in space, leading to selective stimulation of macular gravity receptors (66, 67). This finding was confirmed and extended in further experiments (68, 69) showing that the recorded LC complex neurons, which responded to gravity signals, had the characteristics usually attributed to NE-containing neurons (cf. 19, 22); moreover, some of these neurons could be antidromically activated from the ipsilateral spinal cord at T12-L1, thus belonging to the CS pathway. The labyrinthine input could, in part at least, reach these neurons by utilizing direct afferent projections from the vestibular nuclei to the LC complex (13, 26). The conclusion of these experiments, i.e. that the gravity force which belongs to the terrestrial environment represents the stimulus responsible for tonic discharge of the LC neurons, is supported by the results of experiments performed during the Shuttle mission STS-90, called "Neurolab" (NASA), in which we showed that in albino Fischer 344 rats the expression of immediate early gene proteins (such as the Fos-related antigens, FRA) increased in the LC when linear acceleration increased during the launch and more prominently during the reentry (Pompeiano M. *et al.*, *Acta Otolaryngol., Stockh.*, 2001 in press). It is of interest that the electrophysiological responses of LC neurons to macular signals, observed in decerebrate cats, disappeared during the cholinergically induced cataplectic episodes (67). It appears, therefore, that the inhibitory process which affects the LC neurons during these cataplectic episodes (see above) is responsible for the suppression not only of the resting discharge of the LC neurons, but also of their responses to labyrinth stimulation.

## DYNAMIC CONTROL OF POSTURE DURING VESTIBULAR STIMULATION

Postural adjustments involving the limb and axial (neck) musculature occur by changing head position in space (cf. 74). These vestibulospinal reflexes (VSR) depend, in part at least, on both the static and dynamic response properties of vestibular afferents originating from the utricle and the saccule, the otolith organs of the mammalian labyrinth. These afferents are characterized by a functional "polarization vector" in three-dimensional space, with respect to the coordinates of the animal's head (cf. 21, 83). When this vector is positioned parallel to gravity

by tilting the head there is a maximal output and, when positioned in the opposite direction, a minimal output results. The orientation of the population of polarization vectors in mammals (21, 83) falls into horizontal and vertical planes consistent with the orientation of the sensory hair cells on the surface of the utricular and saccular maculae. Similarly to the vestibular afferents, even the second order vestibular neurons can encode head position in a given direction, thus determining an appropriate reflex control of neck and forelimb extensors (cf. 1 for ref.). Indeed there is evidence that the VSRs are endowed with a high degree of spatial specificity, as shown by the fact that a given muscle is maximally activated by a specific direction of animal tilt (43, 89).

A. *Role of the LVN.* - Experiments performed in decerebrate cats have shown that the VSR elicited by slow rotation about the longitudinal axis of the animal, leading to sinusoidal stimulation of macular, utricular receptors, are characterized by contraction of limb extensors during ipsilateral (side-down) tilt of the animal and relaxation during contralateral (side-up) tilt (43, 44, 75). These postural changes were, in part at least, attributed to the activity of the three-neuronal VSR arc, characterized by primary vestibular afferents, second order VN neurons originating from the LVN and the corresponding limb extensor motoneurons (41). It appeared, in fact, that a proportion of the LVN neurons (8, 76), including those projecting to the lumbosacral segments of the spinal cord (45), responded to the positional signal, during slow rotation of the animal with a response pattern, characterized by an increased discharge during side-down tilt and a decreased discharge during side-up tilt.

B. *Role of the dorsolateral pontine tegmentum.* - In spite of the good postural activity in our decerebrate cats, the gain of the VSR elicited during sinusoidal roll tilt of the animal was very low in both fore- and hindlimb extensors (44, 71). In these instances, the activity of the extensor motoneurons induced by the excitatory VS volleys during side-down tilt was limited by the simultaneous discharge of R-cells, driven in part at least by the recurrent collaterals of the corresponding motoneurons (71). There is now evidence that the R-cells can be influenced not only by the corresponding $\alpha$-motoneurons via the recurrent collaterals, but also by supraspinal sources terminating directly on them (cf. 35, 60). We postulated, therefore, that in addition to the VS pathway, acting directly on ipsilateral limb extensor motoneurons, there were also descending pathways which could modify the response gain of these motoneurons to the excitatory VS volleys by acting on R-cells anatomically linked with them (60).

The results of our experiments indicate that the pathways involved in the gain regulation of the VSR are the CS tract and the medullary RS tract. It has already been reported in Section 1, B (see also Fig. 1) that the CS pathway exerts a facilitatory influence on ipsilateral limb extensor (and flexor) motoneurons by inhibiting, in part at least, the R-cells anatomically linked with them (24, 25). On the other hand, the medullary RS pathway, which is under the inhibitory control of the LC complex acting through the related dorsal pRF, exerts an inhibitory

influence on ipsilateral limb extensor (and flexor) motoneurons by activating, in part at least, the corresponding R-cells (cf. 60 for ref.). We discovered that a large proportion of the presumably inhibitory medullary RS neurons as well as of the LC complex neurons, including the CS neurons projecting to the lumbosacral segments of the spinal cord, responded to animal tilt with a response pattern which was opposite in sign to that of the VS neurons projecting to the same segments of the spinal cord (cf. 62). However, due to reciprocal interaction between the LC complex neurons and the pRF units (59; cf. 33), the activity of the excitatory CS neurons could from time to time predominate over that of the inhibitory RS neurons or *vice versa*.

In precollicular decerebrate cats, in which the high resting discharge of the LC neurons tonically inhibited the pRF neurons and the related inhibitory mRS neurons (66, 67), the amplitude of the EMG responses of limb extensors to sinusoidal tilt of the animal was quite small (44, 71; cf. 65). This finding was attributed to the fact that the R-cells linked with limb extensor motoneurons fired in phase with the corresponding motoneurons during side-down animal tilt, due not only to an increased discharge of the VS neurons (see above) but also to a reduced discharge of the CS neurons, leading to disinhibition of the related R-cells (71). This would increase the functional coupling of these inhibitory interneurons with their own extensor motoneurons, thus reducing the gain of the corresponding VSR. Different results, however, were obtained when in the same preparation the activity of the LC neurons was partially or completely impaired, while that of the pRF neurons and the related inhibitory mRS neurons increased, due to some of the neurochemical procedures described in Section 1, B. In these experiments, the increased discharge of the pontine and medullary reticular neurons could be either moderate to decrease the postural activity (*primary state*) or so prominent to suppress posture (*secondary state*) in the animal at rest. During the *primary state* the gain of the VSR increased (cf. 62). In this instance the R-cells linked with limb extensor motoneurons fired out of phase with respect to the corresponding motoneurons during side-down tilt, due to a reduced discharge of the RS neurons leading to disfacilitation of the related R-cells (72). This would decouple these inhibitory interneurons from their own extensor motoneurons, thus increasing the response gain of limb extensors to labyrinth stimulation. During the *secondary state*, however, the increased discharge of the pRF neurons and the related inhibitory RS neurons was so prominent to suppress not only posture, but also the VSR, due to intense postsynaptic inhibition of the extensor $\alpha$-motoneurons (cf. 62).These findings may, in part at least, explain why elderly people, which undergo atrophic changes of noradrenergic LC neurons (14), also display profound changes in posture and balance.

In conclusion, it appeared that the increased discharge of the noradrenergic LC neurons which occurs after decerebration enhanced the postural activity but actually reduced the gain of the VSR. In contrast, a progressive decrease in discharge of the same neurons, leading either to a reduction or to suppression of posture, increased or decreased the gain of the VSR, respectively. The neuronal circuit made by the noradrenergic LC neurons, and the related cholinergic and/or

cholinoceptive pRF neurons may thus act as a variable gain regulator at the motoneuronal level during the VSR, by modifying the functional coupling of R-cells with the corresponding limb extensor motoneurons. Since the resting discharge of the LC neurons undergoes spontaneous fluctuations during the sleep-waking cycle (3; cf. 22, 33, 50 for ref.), we postulate that this system exerts a prominent role in adapting the gain of the VSR to the animal state.

## CONCLUSIONS

The results of the experiments reported above indicate that the postural activity depends primarily on the discharge of the LVN, whose descending VS projection produces monosynaptic (and polysynaptic) activation of both tonic $\alpha$- and static $\gamma$-motoneurons innervating the ipsilateral extensor musculature. The same pathway also produces disynaptic (and polysynaptic) inhibition of the antagonistic flexor motoneurons. The LVN intervenes not only in the static control of posture (decerebrate rigidity), but also in the dynamic postural adjustments occurring during the VSR.

In addition to the LVN, there are also dorsal pontine tegmental structures, such as the LC complex and the neighboring dorsal pRF, which exert a modulatory influence on static posture, as well as on the dynamic postural adjustments occurring during vestibular stimulation. It is noteworthy that the LC complex, which is made by noradrenergic and NE-sensitive neurons, exerts a facilitatory influence on posture by acting on the spinal cord either directly, through the CS pathway or indirectly, through the dorsal pRF. In particular, the direct CS projection activates the limb extensor motoneurons, but inhibits the corresponding R-cells, thus leading to disinhibition of both the tonic $\alpha$-motoneurons and the static $\gamma$-motoneurons. On the other hand the dorsal pRF, which includes presumably cholinergic and cholinosensitive neurons, is inhibited by the LC complex, but exerts an excitatory influence on medullary inhibitory RS neurons.

Evidence is presented indicating that the resting discharge of the LC neurons, which is very low in the intact animal during quiet waking, increases after decerebration. This effect is likely to depend upon interruption of a supramesencephalic descending pathway, which exerts a tonic inhibitory influence on the noradrenergic LC neurons. The classical $\gamma$-rigidity which occurs after decerebration, can thus be attributed not only to an increased discharge of the CS neurons, but also to an increased noradrenergic inhibition of the dorsal pRF neurons and the related medullary inhibitory RS neurons. The role that these dorsal pontine tegmental structures exert in the static and the dynamic control of posture should be related to the results of experiments showing that the resting discharge of the LC complex neurons and the related pRF neurons undergo reciprocal changes in firing rate leading to fluctuations in posture. These changes occur either in decerebrate cats during the cholinergically induced cataplectic episodes (66; cf. 59), or in intact animals during the episodes of postural atonia related to REM sleep (cf. 33). We postulate, therefore, that the pontine tegmental structures indicated above inter-

vene in adapting to the animal state the amplitude of the postural responses to vestibular stimulation.

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