CONTROL OF LOCOMOTION IN THE DECEREBRATE CAT

PATRICK J. WHELAN*
Department of Physiology and Division of Neuroscience, Faculty of Medicine, University of Alberta, Edmonton, Canada

(Received 10 April 1996)


Only in recent years, however, have the mechanisms been analyzed in detail. Quite a few of these mechanisms have been described using the decerebrate cat. Locomotion is initiated in decerebrate cats by activation of the mesencephalic locomotor region (MLR) that activates the medial medullary reticular formation (MRF) which in turn projects axons to the spinal cord which descend within the ventrolateral funiculus (VLF). The MRF region regulates as well as initiates the stepping pattern and is thought to be involved in interlimb coordination. Afferent feedback from proprioceptors and exteroceptors can modify the ongoing locomotor pattern. Recently, the types of afferents responsible for signaling the stance to swing transition have been identified. A general rule states that if the limb is unloaded and the leg is extended, then swing will occur. The afferents that detect unloading of the limb are the Golgi tendon organs and stimulation of these afferents (at group I strengths) prolongs the stance phase in walking cats. The afferents that detect the extension of the leg have been found to be the length- and velocity-sensitive muscle afferents located in flexor muscles. Plasticity of locomotor systems is discussed briefly in this article. Decerebrate animals can adapt locomotor behaviors to respond to new environmental conditions. Oligosynaptic reflex pathways that control locomotion can be recalibrated after injury in a manner that appears to be functionally related to the recovery of the animal. Copyright © 1996 Elsevier Science Ltd.

CONTENTS

1. Introduction 482
   1.1. Definition of decerebrate preparations 482
2. The control of locomotion by regions of the brainstem 483
   2.1. Introduction 483
   2.2. The subthalamic locomotor region (SLR) 485
   2.3. The mesencephalic locomotor region (MLR) 485
      2.3.1. Inputs to the MLR 486
      2.3.2. The pontomedullary locomotor strip (PLS) 489
   2.4. The medial medullary reticular formation (MRF) 489
      2.4.1. Regulation of ongoing locomotion 490
   2.5. The ventrolateral funiculus (VLF) 490
   2.6. Interneurons activated within the spinal cord 491
      2.6.1. Location of rhythmically active interneurons 492
      2.6.2. Neurotransmitters involved in activating the CPG 492
   2.7. Interaction of posture and locomotion 495
   2.8. Summary 496
3. Afferent control of locomotion 496
   3.1. Introduction 496
   3.2. Reinforcement of the ongoing step cycle 497
   3.3. The control of the stance to swing transition 500
      3.3.1. Extensor muscle afferents 500
      3.3.2. Flexor muscle afferents 500
      3.3.3. Cutaneous afferents 501

*Present address: 755 Medical Sciences Building, University of Alberta, Edmonton, Alberta, Canada T6G 2H7. Tel: (403) 492-1230; Fax: (403) 492-8915; email: pwwhelan@gpu.srv.ualberta.ca.
3.4. A model circuit
3.5. Summary
4. Plasticsity of locomotor pathways involved in the production of locomotion
  4.1. The ability of the decerebrate animal to learn new behaviors
  4.2. Plasticity of the extensor group I pathway
  4.3. Summary
5. Concluding remarks
Acknowledgements
References

ABBREVIATIONS

ACh Acetylcholine
APV 2-amino-5-phosphonovaleric acid
CNQX 6-cyano-7-nitroquinoxaline-2,3-dione
CPG Central pattern generator
DLF Dorsolateral funiculus
DSCT Dorsal spinocerebellar tract
DTF Dorsal tegmental field
EAA Excitatory amino acids
EDL Extensor digitorum longus
EMG Electromyographic
EN Entopeduncular nucleus
ENG Electroneurogram
FRA Flexor reflex afferents
GTO Golgi tendon organ
IP Iliopsoas
LGS Lateral gastrocnemius and soleus
MG Medial gastrocnemius
MLR Mesencephalic locomotor region
mMLR Medial mesencephalic locomotor region
MRF Medial medullary reticular formation
NA Nucleus accumbens
NMDA N-methyl-D-aspartate
PLS Pontomedullary locomotor slice
PPN Pedunculopontine nucleus
SLR Subthalamic locomotor region
STN Subthalamic nucleus
TA Tibialis anterior
VLF Ventrolateral funiculus
VSCT Ventral spinocerebellar tract
VTF Ventral tegmental field

1. INTRODUCTION

It is evident that the reflex, as well as other, phenomena of the mammalian spinal cord present a large field of inquiry, being much more varied and extensive than previous experience had led us to suppose (Foster, 1879, as cited in Liddell, 1960).

The most astonishing thing about walking is how easy it seems. This apparent ease, however, is the result of complex interactions between spinal interneurons, afferent input from the limbs, supraspinal influences from the cortex and the locomotor centers within the brainstem. A great deal of knowledge regarding the control of locomotion has been gathered using the decerebrate cat, which has proved useful because, with appropriate stimulation, fully coordinated stepping can be evoked from all four limbs. In ideal situations, this stepping pattern can be altered by the experimenter from walking to trotting to galloping, simply by increasing the electrical stimulus to the brainstem. Obviously, one would prefer to use the intact animal at all times to study locomotion, but this is not always possible. For example, stimulation of the brainstem can evoke locomotion in a paralyzed animal that allows intracellular recordings to be made in the spinal cord. For ethical reasons, these types of experiments can only be done in reduced preparations such as the decerebrate cat. Thus, the decerebrate locomoting animal enables the testing of some hypotheses in a more rigorous fashion than is possible in intact animals. Naturally, there are disadvantages to the decerebrate cat, the main one being that the locomotor pattern is artificial and constrained when compared to the intact animal. Also, care must be taken when extrapolating the results from decerebrate to intact cats, as the locomotor system may be calibrated differently in the intact animal.

This review will concentrate on locomotion in the decerebrate mammal, in particular the cat. It does not address the problem in a historical context, because many recent reviews have done so already (see Table 1 for reviews). Instead, selected topics in the control of locomotion will be reviewed that have, in the author’s opinion, progressed significantly in the last 15 years. Most of the progress has been made in three areas: (1) the initiation of walking; (2) the afferent regulation of locomotion; and (3) the plasticity of locomotor systems. The organization of the review reflects this progress and a section is devoted to each area mentioned above.

1.1. Definition of Decerebrate Preparations

Different types of locomoting decerebrate cats can be prepared, depending on the level of transection of the neuraxis. In this review, reference will be made to decorticate, premammillary, and postmammillary preparations. The decorticate preparation was characterized initially by Goltz (1869) (as cited by Liddell, 1960). The latest description of decorticate preparations can be found in the methodology of Perret (1976) (cf Bard and Macht, 1958). These are considered generally to be preparations in which the cortex is removed without any particular damage to the thalamus or basal ganglia. The locomotor movements of these preparations are nearly normal and the cats can indeed run and walk without any external assistance.

The second decerebrate preparation encountered in this review is referred to as the premammillary preparation — see slice ‘a’ in Fig. 1(A). A premammillary cat is prepared by making a transection immediately rostral to the superior...
colliculus and continuing rostroventrally to the rostral tip of the mammillary bodies. These animals can walk spontaneously in response to a moving treadmill, and show righting reflexes.

The postmammillary preparation [also referred to as the mesencephalic preparation — see slice ‘b’ in Fig. 1(A)] is made by making a cut just rostral to the superior colliculi and continuing rostroventrally to a point caudal to the mammillary bodies. These cats, in contrast to the previously described preparation, rarely walk spontaneously and usually require either electrical or chemical stimulation of the mesencephalic locomotor region [MLR] of the brainstem to generate stepping movements.

Finally, the last class of decerebrate animal is produced when the transection of the neuraxis is made between the two colliculi [slice ‘c’ in Fig. 1(A)]. This type of cut produces the “classic” decerebrate preparation described in detail by Sherrington (1906). These preparations rarely locomote, due to the high level of extensor tone [termed decerebrate rigidity by Sherrington (1906)] that is produced after the transection is made.

2. THE CONTROL OF LOCOMOTION BY REGIONS OF THE BRAINSTEM

A single wire electrode ... is applied to the cross section of the bulb at calamus scriptorius after removal of the head. Weak faradization, ..., when applied in the region of the funiculus gracilis evokes reflex stepping in the ipsilateral hindlimb; this stepping commences with the flexion of the limb including hip flexion. If the stimulus is weak the [reflex stepping] may be confined to the ipsilateral hindlimb; if strong, stepping of the contralateral hindlimb commencing with extension, occurs also

(Sherrington, 1910b, as cited by Jordan, 1986).

2.1. Introduction

While the central pattern generator contained within the spinal cord can produce the basic locomotor rhythm (Forssberg and Grillner, 1973; Forssberg et al., 1980a, 1980b), brainstem structures are necessary to activate and regulate the rhythm in the intact and decerebrate animal. Since these regions were discovered initially using electrophysiological methods, they were labeled as locomotor regions (Shik et al., 1966a, 1966b). However, it is now known that “locomotor regions” located within the brainstem encompass nuclei that are responsible for the control of many diverse processes (Reese et al., 1995). Thus, the term “locomotor region” is somewhat misleading, although it will be used in this review since it is used widely in the literature. Locomotor regions within the brainstem are classified as such if they contain neurons that, when activated chemically or electrically, lead to the production of locomotion. There are at least four regions of the brainstem that meet these criteria. The first one is the mesencephalic locomotor region [MLR] discovered by Shik et al. (1966a, 1966b), which projects to neurons located in the medial medullary reticular formation [MRF] and then on to interneurons in the spinal cord. The second area is the medial MLR [mMLR] which projects axons along an area of the brainstem known as the pontomedullary locomotor strip [PLS] to the MRF, and forms part of a sensorial activating system that travels along the dorsolateral funiculus [DLF]. Finally, stimulation of the PLS and MRF can elicit bouts of locomotion, although the bouts tend to be uncoordinated and, at times, spastic.

The MRF and MLR receive inputs from many forebrain regions that lead to the production of complex locomotor behaviors. The following are three forebrain pathways that have been described:

1. a projection from the hippocampus and amygdala to the nucleus accumbens (NA) and onwards to the sub-pallidal region and the MLR (Mogenson, 1987);
2. inputs from basal ganglia structures to the MLR (Garcia-Rill, 1986); and
3. inputs from the lateral hypothalamic area to the MLR (Sinnamon, 1993).

While the emphasis in this section is on locomotor areas that initiate locomotion, it is also well known that descending inputs to the spinal cord can modulate the ongoing pattern. For example, inputs from the vestibulospinal, reticulospinal and ru-
brospinal tracts can modulate the amplitude of the electromyographic activity in muscles in a phase dependent manner during walking and in some cases can affect the timing of the rhythm (Russel and Zajac, 1979). Furthermore, electrical stimulation of areas of the brainstem such as the locus coeruleus, raphe nucleus (Noga et al., 1992) and the cuneiform nucleus (Noga et al., 1995b; Perreault et al., 1994a) can modulate the amplitude of group I and II field potentials. These findings suggest that regions of the brainstem.
brainstem not only provide the tonic descending drive necessary to activate the locomotor pattern generator, they can also optimize reflex pathways.

2.2. The Subthalamie Locomotor Region (SLR)

A cat that is decerebrated with a transection starting just rostral to the superior colliculus and extending rostroventrally to the rostral tip of the mammillary bodies produces a premammillary preparation that can spontaneously elicit bouts of locomotion lasting from minutes to hours. During times when these animals are not spontaneously locomoting, electrical stimulation of an area known as the subthalamie locomotor region (SLR) can evoke locomotion in the premammillary cat. The SLR region was described by Orlovsky (1969) as being centered on stereotaxic coordinates A9, L1—2 and H3, with a spherical diameter of 1 mm in the region of the H1 and H2 fields of Forel (Fig. 1) (cf Grossman, 1958). If a thin sliver of tissue approximately 3 mm thick, containing the SLR region, is shaved off the brainstem, locomotion ceases to occur spontaneously and stimulation of the MLR region is required. Lesion studies in intact cats have indicated that the SLR is important for the initiation of goal directed locomotion. After a lesion of an area of the diencephalon corresponding to the SLR, the MLR region, is shaved off the brainstem, locomotion ceases to occur spontaneously and stimulation of the MLR region is required. Lesion studies in intact cats have indicated that the SLR is important for the initiation of goal directed locomotion. After a lesion of an area of the diencephalon corresponding to the SLR, the animals initially are unable to commence voluntary locomotion, although they do respond to noxious stimuli. Within 2—3 weeks after lesioning, these animals eventually recover the ability to initiate goal-directed locomotion, demonstrating that other structures eventually compensate for the lesion (Sirota and Shik, 1973; cited by Shik and Orlovsky, 1976; cf Bard and Macht, 1958). Further support for the role of the SLR in initiating goal-directed locomotion was obtained by stimulating the SLR region in intact cats (Mori et al., 1989). When the SLR was stimulated, the cat typically was aroused and orientated itself to the surroundings by raising its head and looking around [Fig. 8(D)]. A few seconds after the beginning of SLR stimulation, the cat started to walk slowly and looked around repeatedly. According to Mori et al. (1989), SLR-induced locomotion was indistinguishable from spontaneous locomotion. It is not known what connections from the SLR may produce this complex behavior. It is likely to be due to the activation of other rostral and caudal areas, since stimulation of the SLR typically requires some time before it produces locomotion, suggesting that reverberating circuits are activated.

Garcia-Rill (1986) raised the possibility that stimulation of the SLR may be activating fibers of passage arising from the entopeduncular nucleus (EN) and substantia nigra which project to the thalamus and directly to the MLR. Stimulation of the SLR in the decerebrate cat is thought to cause a disinhibition of the MLR. However, while the SLR may project to the MLR region, the integrity of the MLR is not necessary for SLR-evoked locomotion to occur in premammillary cats (Sirota and Shik, 1973, as cited by Shik and Orlovsky, 1976). This suggests that descending projections from the SLR may activate other locomotor areas in the brainstem in addition to the MLR, such as the MRF. Furthermore, this observation supports the proposal that activation of multiple sites within the brainstem are necessary for locomotion to occur (Garcia-Rill, 1991).

2.3. The Mesencephalic Locomotor Region (MLR)

Locomotion can be initiated in the decerebrate cat by electrically stimulating an area of the brainstem [Fig. 1(B)] close to the cuneiform nucleus known as the mesencephalic locomotor region (MLR) (Shik et al., 1966a, 1966b). The MLR region is an important integrative centre in the brainstem. It receives information from many areas of the brain, including the basal ganglia (Mogenson, 1990), the limbic system (Garcia-Rill, 1986), and the frontal cortex (Divac et al., 1978). Graded electrical stimulation of the MLR in the decerebrate cat is followed by an increase in extensor tone and stepping that often takes a number of seconds to appear. The locomotion produced by stimulation of the MLR can be quite realistic. Many different gait patterns are produced (walking, trotting, galloping) depending on the strength of the stimulus. The optimal region in the brainstem for eliciting locomotion is a 2 mm² area located just beneath the inferior colliculus (Fig. 1B) and encompassing the pedunculopontine nucleus (PPN), the caudal end of the cuneiform nucleus, and the brachium conjunctivum (Horsley-Clarke coordinates P2: L4: H6). It is controversial whether the anatomical location of the MLR is within the cuneiform nucleus or the PPN (Inglis and Winn, 1995; Reese et al., 1995). This issue is still not resolved, although evidence using activity-dependent dyes and electrophysiological techniques points to the cuneiform nucleus as being a more likely candidate than the PPN in the initiation of locomotion (Inglis and Winn, 1995; Shojania et al., 1992; Moon-Edley and Graybiel, 1983; Jordan personal communication). However, the PPN may be involved in the initiation of locomotion under certain conditions such as when an intact animal is startled by an auditory stimulus (Garcia-Rill, 1991). One potential problem in establishing the anatomical location of the MLR is that there are direct connections from neurons in lamina I of the spinal cord to this area (Hylden et al., 1985). Thus it is not known whether electrical stimulation of the MLR may antidromically activate cells in lamina I and indirectly affect the operation of the locomotor pattern generator (Reese et al., 1995).

In addition to the MLR region, there are at least two other areas in close proximity that can elicit locomotion. The first area lies medial to the MLR and is located close to the spinal trigeminal nucleus (Shefchyk et al., 1984). It is thought that this area is continuous with Probst’s tract and forms the pontomedullary locomotor strip [Fig. 2(A); see Section 2.3.2]. The second region is located dorsal to the classic MLR in the inferior colliculus (Skinner and Garcia-Rill, 1990). In comparison with the other two areas very little is known about its function or its anatomical connections.

Interestingly, similar locomotor areas have been described in different vertebrate species such as the rat (Garcia-Rill et al., 1990; Bedford et al., 1992; Coles et al., 1989; Parker and Sinnamon, 1983),
486  

I. Whelan

guinea pig (Marlinskii and Voitenko, 1992), stingray (Bernau et al., 1991), lamprey (McClellan, 1988; McClellan and Grillner, 1984), rabbit (Corio et al., 1993), monkey (Eidelberg et al., 1981a; Hultborn et al., 1993) and the bird (Steeves et al., 1987; Sholomenko et al., 1991). There are also clinical studies suggesting the existence of similar areas in the adult human (Caplan and Goodwin, 1982; Masdeu et al., 1994; Zweig et al., 1987; Hanna and Frank, 1995) and the anencephalic infant (Peiper, 1961 as cited by Forssberg, 1985). These and other commonalities amongst disparate vertebrates raise the hope that advances currently being made on simple in vitro preparations such as the lamprey (Grillner et al., 1995) can be extrapolated to higher vertebrates.

2.3.1. Inputs to the MLR

Until recently it was not known whether cell bodies within the MLR were being activated to produce locomotion, or if the electrical stimulation was activating fibers that passed through the MLR region. Evidence suggesting that neurons within the MLR are stimulated has been obtained by chemically activating the MLR/PPN region using agents that act postsynaptically and which lead to the activation of:

Fig. 2. (A) The pathway from the MLR region passes mainly to the MRF region of the brainstem. After synapsing in the MRF area, the axons travel caudally through the ventrolateral funiculus (VLF) and synapse with interneurons in the lumbar spinal cord. (B) The medial MLR has been discovered only relatively recently and is considered to be distinct from the classical MLR. It is located in close proximity to the trigeminal system and nucleus and is thought to form part of a general sensory activating system. It travels through an area of the brainstem called the pontomedullary locomotor strip (PLS) (Probst's tract) and descends via the dorsolateral funiculus (DLF) to the dorsal horn of the spinal cord. The PLS is thought also to send collaterals to the MRF region. Figure reproduced from Mori et al. (1992) with permission. Abbreviations: SLR, subthalamic locomotor region; MLR, mesencephalic locomotor region; mLRLR, medial mesencephalic locomotor region; PPN, pedunculopontine nucleus; DTF, dorsal tegmental field; VTF, ventral tegmental field; CNF, cateniform nucleus; I.C., locus coeruleus; NRPo, nucleus reticularis pontis oralis; NRPa, nucleus reticularis pontis centralis; NRGc, nucleus reticularis gigantocellularis; NRMc, nucleus reticularis magnocellularis; th., thoracic; lumb., lumbar.
depression of locomotor activity. Chemical activation of the MLR in the postmammillary cat (Fig. 3) by NMDA (Garcia-Rill et al., 1990) and GABA antagonists such as bicuculline and picrotoxin (Garcia-Rill et al., 1985) can evoke locomotion that is similar to that evoked by electrical stimulation. Locomotion evoked by infusion of picrotoxin or bicuculline will cease if either GABA or muscimol is infused onto the MLR (Garcia-Rill et al., 1985; cf Brudzynski et al., 1986). Thus, activation of the MLR is controlled by a mixture of inhibitory and excitatory inputs. The origin of these inputs to the MLR is diffuse, and locomotion may be controlled by an activation of many systems in parallel (Reese et al., 1995; Inglis and Winn, 1995). In this review, two forebrain regions that project onto the MLR, the basal ganglia and the NA, will be discussed. Stimulation of the lateral hypothalamic area (LHA) which projects to the MLR and onto the reticular formation also can evoke locomotion (Sinnammon, 1993). While the LHA is located in close proximity to the SLR (Section 2.2), it has been suggested that the more lateral regions of the hypothalamus may be involved in mediating appetitive responses while the area surrounding the zona incerta (encompassing the SLR) may be responsible for the control of exploratory locomotion (Sinnammon, 1993).

The basal ganglia are involved intimately in the production of movement. This is evident in patients who suffer from Parkinson's disease, characterized by akinesia and abnormalities of gait. Classically, the basal ganglia have been thought to influence locomotion by a pathway that travels from the cortex through the striatum and pallidum and finally back to the cortex via the thalamus. However, the basal ganglia do have direct connections to the MLR and they are involved in more direct way. Garcia-Rill and colleagues have described some of the connections between the basal ganglia nuclei and the MLR (for a review, see Garcia-Rill, 1986). As mentioned earlier, a premammillary preparation can spontaneously initiate locomotion, while a postmammillary cat loses this ability and usually requires chemical or electrical stimulation to walk. The only structure rostral to the MLR in a postmammillary preparation that is known to project afferents to the MLR is the substantia nigra pars reticulata (SNpr) which is part of the basal ganglia. Since neurons within the MLR can be activated by GABAergic antagonists, it has been suggested that the MLR in the premammillary cat is under a strong inhibitory influence from the SNpr [Fig. 4(B)]. Indeed, retrogradely labeled neurons have been found in the SNpr after a fluorescent dye was applied to the MLR region (Garcia-Rill et al., 1983a, 1983b) and intracellular recordings from cells in the SNpr have shown that they can be activated antidromically upon stimulation of the MLR (Garcia-Rill, 1983). A puzzling question is that of whether structure is contained within the small wedge of tissue [between slices 'a' and 'b' in Fig. 4(A)] that allows spontaneous walking to occur in the premammillary cat. The only known structure that has connections with the SNpr and is located within this wedge of tissue is the subthalamic nucleus (STN). Preliminary evidence has demonstrated that the SNpr contains GABA receptors and that GABA antagonists applied to the SN can block locomotion (Garcia-Rill and Skinner, 1986). So this has led to the idea that the subthalamic nucleus inhibits the SNpr, which allows the MLR to become active [Fig. 4(B)]. While this hypothesis is very appealing, it is unclear how this inhibition of the SNpr could occur, since Hammond et al. (1983) has documented that there is a substantial excitatory connection to the substantia nigra pars reticulata. Furthermore, although Garcia-Rill et al., 1983a) found a projection from the SNpr to the MLR region, less than 10% of SN neurons were activated antidromically by stimulation of the MLR, suggesting that the projection is very sparse. Another area of the basal ganglia that has been proposed to affect the activity of the MLR is the EN, equivalent to the globus pallidus internus in primates. The EN has excitatory and inhibitory projections to the STN, SN and the MLR (Garcia-Rill, 1983). Some of the EN axons travel through a region of the diencephalon known as the zona incerta which contains the SLR (Garcia-Rill, 1986; Grossman, 1958; Waller, 1970). If electrical stimulation were primarily activating the EN fibers, locomotion could be produced either by direct activation of the MLR.
(possibly by a release of substance P) or indirectly by inhibition of the SN (Garcia-Rill et al., 1985; Garcia-Rill, 1983).

Another major input to the MLR arises from the limbic system (Mogenson, 1987, 1990). It is believed that this pathway integrates food procurement, predator escape, and other adaptive behaviors into the locomotor behavior of the animal (all studies performed using the rat). The projection from the limbic system to the MLR is indirect and is mediated

---

Fig. 4. Simplified diagrams indicating the inputs from the limbic system (A) and the basal ganglia (B) onto the MLR region. Activation of the nucleus accumbens mainly occurs from excitatory activity from the hippocampus and amygdala. The nucleus accumbens has been shown to project to the MLR both indirectly (heavy lines) and directly (dashed line). The main pathway is the indirect pathway. (B) The MLR is affected by activity in the basal ganglia. The MLR receives tonic GABAergic inhibition from the substantia nigra which, in turn, receives GABAergic projections from the subthalamic nucleus (STN). Activity of the STN causes a disinhibition of the MLR, which presumably leads to the production of locomotion. The entopeduncular nucleus projects both excitatory and inhibitory afferents to the SN and MLR. The dotted lines indicate the hypothesized function of the EN. Activity of the EN modulates activity in the SN and MLR which enable the production of locomotion by the MLR (see text for more details).

Abbreviations: EN, entopeduncular nucleus; SN, substantia nigra; MLR, mesencephalic locomotor region; PPN, pedunculopontine nucleus; VTF, ventral tegmental field.
by the NA, which is part of the ventral striatum. Under normal situations, tonic inhibition of the NA by mesolimbic dopaminergic afferents from the ventral tegmental area (VTA) results in the initiation of movement in the rat by an indirect activation of the MLR [Fig. 4(A)] (Mogenson and Wu, 1986; Brudzynski et al., 1993). When the amygdala or hippocampus is active, glutaminergic projections onto the NA cause an increase in locomotor behavior in freely moving rats (Wu et al., 1993). These projections synapse on D_{2} receptors located in terminals of the mesolimibic system within the NA and cause an increase in the inhibitory dopaminergic output from the terminals, allowing the MLR to become active. The NA exerts its effects on the MLR indirectly via an inhibitory GABAergic connection to the ventral globus pallidus (sub-pallidal region). Finally, excitatory connections from the sub-pallidal region pass through the zona incerta (the SLR) and which terminates onto the MLR (Brudzynski et al., 1993). Evidence suggesting this pathway exists is based on these findings when locomotion is elicited by NA or limbic system activation: (1) locomotion can be attenuated by cooling of the zona incerta region (Mogenson, 1987); (2) application of GABA to the ventral globus pallidus (subpallidal) (Jones and Mogenson, 1980) or the MLR region results in a reduction in locomotor behavior; (3) picrotoxin (GABA antagonist), when applied to the subpallidial region, causes locomotion to increase (Mogenson and Nielson, 1983); and (4) application of procaine (activity blocker) or cobalt chloride to the MLR region causes locomotion evoked by limbic system activation to be reduced (Brudzynski et al., 1993).

It is important to realize that connections to and between nuclei of the brainstem are diverse and often diffuse. In light of this, Garcia-Rill (1991) has suggested that stepping movements produced by activation of “locomotor regions” occur by recruitment of many sites within the brainstem. This proposal is supported by these observations: (1) trains of stimuli need to be used when stimulating locomotor regions; (2) it usually takes 2–3 sec for locomotion to occur; (3) while the MLR region receives many diverse inputs, locomotion can be produced if this area is lesioned; and (4) stimulation of other areas of the brainstem, such as the mMLR, the MRF, PLS and SLR can elicit locomotion.

2.3.2. The Pontomedullary Locomotor Strip (PLS)

The PLS consists of a continuous strip of tissue that extends from an area close to the spinal trigeminal nucleus, continues caudally to the medulla and projects to the dorsolateral funiculus (DLF). It is considered to be anatomically equivalent to Probst’s tract, which carries spinal and trigeminal afferents (Garcia-Rill, 1986). Stimulation of the PLS in a decerebrate cat can evoke bouts of locomotion similar to MLR-evoked stepping. It was proposed initially that the PLS carried fibers from the MLR region through to the DLF (Kazennikov et al., 1979, 1983, 1988). It now appears that the PLS receives afferent input from the medial MLR (mMLR) and projects mainly to the MRF (Shefchyk et al., 1984) [Fig. 2(B)], because cooling of the MRF blocks PLS-evoked locomotion while lesions of the DLF do not (Noga et al., 1991). However, since the PLS can be activated chemically by glutamic acid or picrotoxin (Fig. 3), it must contain neurons as well as axons (Noga et al., 1988). It has been proposed that the medial MLR and PLS form part of a sensorial activating system that is similar to the activation of the spinal central pattern generator (CPG) by tonic stimulation of dorsal roots or by pinching of the tail (Jordan, 1986; Noga et al., 1988; Garcia-Rill, 1986). This has been suggested in light of the following observations: (1) the effective drug-inducing sites within the PLS were located within the trigeminal nucleus; and (2) infusion of picrotoxin into the PLS region allowed mild stimulation of regions innervated by the trigeminal nerve (Pinna, Mandibulum) to evoke treadmill locomotion in the decerebrate cat (Noga et al., 1988).

2.4. The Medial Medullary Reticular Formation (MRF)

One of the main questions that arose from past MLR experiments was that of which pathway in the brainstem was being activated that led to the triggering of the locomotor pattern generator in the spinal cord. By using a combination of chemical, cooling, lesion and electrophysiological techniques it has been demonstrated that the MLR projects to an area of the medial medullary reticular formation (MRF) [Fig. 2A]. The MRF neurons project axons to the intermediate and ventral areas of the spinal cord gray matter and descend within the ventrolateral funiculus (VLF). The MRF receives a vast amount of information from the cerebellum, cortex, basal ganglia and the MLR (Armstrong, 1986). It is also the last integrative point before the descending locomotor command signal is relayed via the VLF to the interneurons in the spinal cord (Noga et al., 1991). The region of the MRF in the cat that can evoke locomotion (P4–P14 and L0–L2, Noga et al., 1988) includes the nucleus gigantocellularis and nucleus tegmenti reticularis. Electrical (Mori et al., 1978; Garcia-Rill and Skinner, 1987a, 1987b) or chemical (Noga et al., 1988; Garcia-Rill et al., 1985) stimulation of the MRF can induce locomotion in decerebrate cats, but the ensuing rhythm is less regular and reliable than that evoked from the MLR region (Jordan, 1986). Cooling or chemical stimulation of the MRF has indicated that it is an important region for the initiation of locomotion. Cooling of the MRF region in postmammillary cats causes stepping to cease during both MLR-evoked and spontaneous stepping (Shefchyk et al., 1984). Furthermore, the effective sites within the MRF for evoking locomotion happen to receive inputs from the MLR (Garcia-Rill and Skinner, 1987a, 1987b; Steeves and Jordan, 1984) as well as from areas involved in the control of posture (Mori et al., 1992; Mori, 1987; Section 2.7). Pharmacological methods demonstrate that glutamic acid (Noga et al., 1988), acetylcholine (ACh) and substance P (Garcia-Rill and Skinner, 1987a) can evoke locomotion when applied to the MRF in the mesencephalic cat. Application of picrotoxin reduces the threshold for evoking locomotion by electrical stimulation of the
MRF but, in isolation, it is not capable of evoking locomotion. The chemical activation of the MRF demonstrates that activation of cell bodies, and not fibers of passage, can evoke locomotion. One would expect from these studies that neurones containing substance P, ACh or glutamate would exist within the MLR, however, the experimental evidence is mixed. There is little evidence for the existence of ACh or substance P neurones in the MLR (Leger et al., 1981; Lee et al., 1986), although Garcia-Rill and Skinner (1987a, 1987b) have obtained some evidence for the existence of cholinergic neurones contained within the PPN.

Similar to the MLR region, MRF locomotor areas have been found in other species such as the lamprey (McClellan and Grillner, 1984; McClellan, 1988), stingray (Livingston and Leonard, 1990; Bemau et al., 1991), bird (Steeves et al., 1987; Sholomsko et al., 1991) and rat preparations (Kinyo et al., 1990).

2.4.1. Regulation of Ongoing Locomotion

The MRF can regulate as well as initiate a locomotor pattern. Orlovsky (1970) found that in postmammillary and premammillary cats, cells of the reticular formation (located in the medial longitudinal fasciculus) responded mainly during the flexor portion of the step cycle, and that stimulation of this region increased the amplitude of the flexor bursts during swing (Orlovsky, 1972a). More recent studies in premammillary and intact cats have shown that recording from cells in the MRF show considerably more complex response characteristics (Drew and Rossignol, 1984; Drew et al., 1986; Drew, 1991b). In premammillary decerebrate cats (Drew and Rossignol, 1984), cells in the MRF were found that fired phasically with high firing rates during the stance and swing phase of the step cycle.

Since MRF neurones can affect different muscles in all limbs in a phase-dependent manner, it has been proposed that the descending signal is sculpted by the actions of the central pattern generator (CPG) (Drew et al., 1986). It is not known at present how this is accomplished; however, gating of the descending input could occur by presynaptic inhibition of the monosynaptic projecting MRF fibers, or by postsynaptic modulation of the motoneuron and/or modulation of interneuronal connections. Output from the CPG could provide the phasic signal that allows this to occur (cf Floeter et al., 1993).

It was discovered recently that the phasic firing patterns of MRF cells are qualitatively similar in fivectively locomoting cats that lack phasic afferent input (Perreault et al., 1993). These data demonstrate that the phasic modulation of neurons within the MRF is, to some extent, produced centrally. The phasic modulation of reticulospinal neurones is dependent on the integrity of the ventral spinocerebellar tract (VSCT). The VSCT carries information to the cerebellum regarding the activity of rhythmically active interneurons within the spinal cord and reflects the activity of the locomotor CPG (Arshavsky et al., 1972a, 1972b, 1972c). Even though MRF neurones are rhythmically active during fictive locomotion, evidence suggests that afferent (especially cutaneous) input has access to these neurones (Shimamura et al., 1982, 1985; Shimamura and Kogure, 1979, 1983; Eccles et al., 1975; Drew et al., 1986). Shimamura and colleagues have shown (Shimamura and Livingston, 1963) that there is a spino-bulbar-spiral reflex pathway which is activated mainly by ascending cutaneous input from the limbs (Shimamura and Kogure, 1979, 1983) and which primarily augments the flexor burst in premammillary cats (Shimamura et al., 1982; Shimamura et al., 1990). Supporting evidence for afferent regulation of MRF cells was obtained by Drew et al. (1986) from intact walking cats. In these animals, MRF cells that fired in response to light touch from many areas of the hindlimb and trunk were recorded at rest.

One of the functional roles that has been suggested for the MRF is that it may be involved in interlimb coordination during normal walking (Drew et al., 1986; Shimamura and Kogure, 1983). This is based on evidence which shows that microstimulation of the MRF region using short stimulus trains can produce phase-dependent activity in muscles in all four limbs that is incorporated into the ongoing step cycle in premammillary cats (Drew and Rossignol, 1984), postmammillary (Perreault et al., 1994b) and intact cats (Drew, 1991b; Drew and Rossignol, 1990a, 1990b). Using longer stimulus trains can increase the duration of the ipsilateral swing phase, with a corresponding increase in the contralateral stance phase (Drew and Rossignol, 1984; Drew, 1991b; cf Russel and Zajac, 1979), resulting in a change in the timing of the step cycle. In support of these findings, Shimamura and Kogure (1983) illustrated that maximum firing of reticulospinal cells was dependent on the correct position of all limbs in relation to each other in premammillary cats.

2.5. The Ventrolateral Funiculus (VLF)

In the cat and other species (Steeves et al., 1987; Webster and Steeves, 1991; Magnuson et al., 1995; Garcia-Rill et al., 1990; Eidelberg et al., 1981b), the projections from the MRF region to the spinal cord descend in the VLF of the spinal cord [Fig. 2(A) and Fig. 5]. Orlovsky (1969) found that there was an increase in impulse traffic in the VLF after stimulation of the MRF in decerebrate cats. Furthermore, in the decerebrate cat, the integrity of the VLF tract is essential for the production of locomotion (Afelt, 1974; Steeves and Jordan, 1980; Eidelberg et al., 1981b), while lesioning of the dorsolateral tract containing the descending tract from the PLS does not affect the ability to evoke locomotion (Noga et al., 1991). In intact cats, Eidelberg (1981) found that the recovery of locomotion was dependent on the ventrolateral quadrant of the spinal cord being intact. However, recent experiments which have lesioned areas of the VLF and/or DLF have found that lesions of the DLF can have large effects on interlimb coordination in intact animals (Bem et al., 1995; Gorska et al., 1993). Similar findings have been made by Brustein et al. (1995), in which intact animals with extensive lesions of the VLF regained the ability to walk. These findings suggest that there may be parallel pathways that can trigger or enable the pattern generator for locomotion. However, it must be kept in mind in any
Fig. 5. Effects of reversible cooling of the dorsal columns, DLF, or VLF of the spinal cord on hindlimb locomotion elicited by stimulation of the ipsilateral PLS at the P17 level [solid lesion site indicated in (I)]. (A)-(C) Illustrate the responses produced by stimulation of the PLS prior to, during and following cooling of the dorsal columns to a probe-tip temperature of –3°C. The effects of cooling the DLF (1°C) and VLF (6°C) are illustrated in (D) and (G), respectively. The extent of fiber (hatched) and synaptic (stippled) is estimated in (I) for each of the trials. Letters beneath spinal cord sections indicate the corresponding cooling trials in (B), (D) and (G). The PLR stimulation parameters were 30 Hz, 0.5 msec duration (all trials). Modified from Noga et al. (1991), with permission. Abbreviations: PLS, pontomedullary locomotor strip; DLF, dorsolateral funiculus; VLF, ventrolateral funiculus.

lesion study that reorganization of the CNS is likely to be taking place (Devor and Wall, 1978; Goldberger and Murray, 1988; Mendell, 1984; Kandel, 1981), so any results gained must be interpreted cautiously.

2.6. Interneurons Activated within the Spinal Cord

It is currently unknown which neurotransmitters are released at the terminals of the VLF axons, although recent evidence from the neonatal rat strongly suggests that it may be glutamate (Elliot and Wallis, 1993; Magnuson et al., 1995; Wallis and Wu, 1993). Furthermore, it is not known which interneurons in the spinal cord receive the VLF afferents and whether they form part of the CPG. In the last 10 years, some progress has been made on two fronts: (1) the location of the interneurons that are rhythmically active during MLR stepping, and (2) which neurotransmitters may be involved in transmit-
ting the descending command for evoking locomotion.

2.6.1. Location of Rhythmically Active Interneurons

Gaining knowledge of where rhythmically active interneurons exist that could form part of the spinal CPG is one of the first steps towards understanding the circuitry involved in the production of a locomotor pattern. As mentioned by Noga et al., 1995a), there have been many studies which have documented the occurrence of rhythmically active interneurons in the spinal cord during evoked locomotion (Arshavsky et al., 1972a, 1972b; Orlovsky and Feldman, 1972; Floeter et al., 1993; Feldman and Orlovsky, 1975; Edgerton et al., 1976; Baev et al., 1979; McCrea et al., 1980; Noga et al., 1987; Pratt and Jordan, 1987; Hishinuma and Yamaguchi, 1990; Ichikawa et al., 1991; Viala et al., 1991; Yamaguchi, 1991, 1992), but only a few types of spinal neurons have been examined in correlation with activation of the MLR or the cuneiform nucleus (Kazennikov et al., 1979, 1983; Edgley et al., 1990; Jankowska and Noga, 1990; Shechky et al., 1990; Noga et al., 1995a). Over the last 10 years, two innovative applications of established techniques have been used in the de cerebrate cat to localize rhythmically active interneurons.

The first technique (Noga et al., 1995a) combined the use of cord dorsum and focal recordings of extracellular field potentials (Skinner and Willis, 1970; Fu et al., 1974; Skinner and Remmel, 1978) using isopotential maps (see Willis, 1980, for a review) to localize areas of rhythmic neuronal activity within the cat spinal cord upon stimulation of the MLR region. Since this technique is relatively new, the methods used will be outlined in some detail. When fictive locomotion was evoked using MLR stimulation, the intraspinal field potentials recorded in the spinal cord were sampled at evenly spaced points (every 250 um) in both the horizontal and vertical planes using sharp microelectrodes. The average amplitude of these intraspinal field potentials was then recorded at fixed latencies triggered off of the onset of the MLR stimulus using a window discriminator. A matrix of intraspinal amplitudes was then assembled that correlated to fixed points in the white and gray matter of the spinal cord. After using a spline function to generate a matrix of higher resolution, lines of equal amplitude were joined to one another creating an isopotential contour effect. Finally, the isopotential maps were transposed onto digitized sections of the spinal cord (points in the matrix were identified by electrode tracks in the spinal cord) to generate the pictures in Fig. 6. Using this method of isopotential mappings in the fictively locomoting cat, monosynaptic activation of interneurons by MLR stimulation has mainly been confined to lamina VII (Noga et al., 1995a). Disynaptic innervation has mainly been localized to laminae VIII, IX and X (Noga et al., 1995a).

The second method that has been used in the de cerebrate cat with some success has been the use of c-fos, an activity-dependent marker, to identify visually neurons that are active during locomotion (Carr et al., 1995; Carr et al., 1994; Dai et al., 1990) or scratching (Barajon et al., 1992). Most c-fos immunoreactive neurons were found to be distributed in medial laminae VI and VII and in laminae VIII and X during MLR-evoked walking. This result is similar to that reported for the distribution of c-fos immunoreactive neurons during fictive scratching (Barajon et al., 1992) and qualitatively matches that observed using isopotential mapping techniques (Noga et al., 1995a).

In summary, localization of rhythmically active interneurons in fictively locomoting animals is usually confined to the intermediate and ventral quadrants of the spinal cord (Noga et al., 1995a; Carr et al., 1995; Kjaerulf et al., 1994; Ho and O Donovan, 1993 (embryonic chick)) and is distributed along the lumbar sacral spinal cord (Deliagina et al., 1984; Grillner and Zangger, 1984). In all of the studies mentioned thus far, it must be realized that the existence of these rhythmically active interneurons does not imply that they form part of the spinal CPG. More research on the identification of these neurons and their synaptic inputs must be completed before any firm conclusions can be made on this issue.

2.6.2. Neurotransmitters Involved in Activating the CPG

For many years, it was thought that monoaminergic pathways were responsible for the activation of the spinal CPG because l-DOPA (a precursor for dopamine and noradrenaline) could initiate locomotion in acute cats that had a transected spinal cord (Grillner, 1973). Furthermore, noradrenaline was thought to be especially important because: (1) clonidine (a noradrenergic agonist) mimicked the effects of l-DOPA in spinal animals (Forssberg and Grillner, 1973); and (2) when the enzymatic steps between l-DOPA, dopamine and noradrenaline were blocked, the actions of l-DOPA could be prevented (Andén et al., 1966). However, Steeves et al. (1980) found that depletion of noradrenaline and serotonin in cats did not abolish locomotion, indicating that other neurotransmitters were at least partly responsible for triggering the locomotor rhythm. It has since been suggested that the noradrenaline and serotonin may act as enablers of the locomotor pattern and not initiators (Harris-Warrick, 1988).

One class of neurotransmitters capable of eliciting a locomotor rhythm in a variety of preparations is the excitatory amino acids (EAA). The EAA agonists, such as N-methyl-D-aspartate (NMDA), have been found to elicit a locomotor rhythm in a variety of preparations including the lamprey (Grillner et al., 1981; see Grillner et al., 1995, for a review), the tadpole (Dale and Roberts, 1984), neonatal rat (Kudo and Yamada, 1987; Cazalets et al., 1992) and mudpuppy (Wheatley et al., 1992). A major obstacle that existed in extrapolating this work to the intact animal was that drugs that antagonize or agonize the EAA's cannot cross the blood–brain barrier. This problem was addressed recently by Douglas et al. (1993), who developed a method for the intrathecal injection of drugs directly into the sub-arachnoid space of the lumbar spinal cord in cats. By adding these drugs during MLR-evoked walking, it was possible to see what effects they had on the stepping
Fig. 6. Localization of interneurons using isopotential mapping of extracellular potentials. The following figures [(A) and (B)] illustrate field potentials (left hand traces) and isopotentials maps on the right from two separate experiments. (A) Amplitude measurement latencies following the MLR stimulus are indicated as numbered arrowheads and correspond to the numbered isopotential maps on the right. Large negative current sinks (solid isopotential lines) are evident in laminae VII–X. The earliest field potentials were generated in the intermediate areas (laminae VI and/or VII) with later field potentials being generated in laminae VIII, IX or X as cells in the ventral horn and around the central canal displayed increased activity. In (A), the foci of positivity were localized to the medial aspect of laminae II, III, IV and VI and to the dorsal columns. In (B), foci of positivity were apparent to the medial part of lamina VI and to the middle aspect of lamina VII. Modified from Noga et al., 1995a), with permission.
When 2-amino-5-phosphonovaleric acid (APV), a specific NMDA antagonist, was injected into the spinal cord, the ensuing rhythm in the hindlimbs evoked by MLR stimulation was blocked [Fig. 7(C)]. Upon washout of APV, the rhythm resumed [Fig. 7(D)]. Application of 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) (a non-NMDA glutamate antagonist) had similar effects to APV, indicating that at least two glutaminergic receptor pathways were contributing to the initiation of locomotion. When NMDA was added to the spinal cord, bouts of locomotor activity were generated; however, they differed from that produced by MLR stimulation as the flexor and extensor electroneurogram (ENG) bursts occurred synchronously. On the other hand, when NMDA was added with dihydrokainic acid (DHK), which is an EAA uptake blocker, the locomotor pattern was improved greatly and produced an alternating pattern that was comparable to that produced by MLR stimulation. These findings strongly suggest that glutamate contributes to the production of the locomotor pattern in cats.

There are two ways in which locomotion can be evoked by glutaminergic agonists. Firstly, the glutaminergic agonists that are released intrathecaclly activate the glutaminergic receptors that receive axons from the descending reticulospinal fibers. Although the neurotransmitters that are released from the terminals of the reticulospinal axons that descend from the MRF have not been identified, it is thought that they are probably glutaminergic. This assumption is based mainly on studies from in vitro models such as the lamprey (Ohta and Grillner, 1989; Grillner et al., 1995) and neonatal rat (Hockman et al., 1994; Magnuson et al., 1995; Kjaerulf et al., 1994). Secondly, the addition of glutaminergic agonists (or antagonists) causes a generalized excitation of the interneurons in the spinal cord that are normally rhythmically active during MLR-evoked locomotion. It is known that large areas of the spinal cord contain neurons that are rhythmically active during MLR-evoked walking (Noga et al., 1995a) and that there is a wide distribution of EAA receptors in the spinal cord (Mayer and Westerbrook, 1987). In support of this, Douglas et al. (1993) observed both locomotor and paw-shaking motor patterns when DHK and NMDA were added intrathecally, which suggested that the EAA agonists were exciting two sets of interneuronal networks each responsible for producing a different behavior.
2.7. Interaction of Posture and Locomotion

Normal stepping does not occur without postural corrections that allow the animal to maintain its balance and stability. Even in the decerebrate cat, postural changes occur before an animal begins to locomote (Takakusaki et al., 1993; Oka et al., 1993). Before locomotion occurs in a cat, there is typically an increase in extensor tone that can, at times, be large enough to support an animal's weight. Using walking decerebrate and intact cats, Mori and colleagues have discovered two regions within the brainstem that influence the level of postural tone (Mori, 1987; Mori et al., 1992). Stimulation of an area within the dorsal tegmental field (DTF) of the brainstem caused a reduction in extensor tone, while stimulation of the ventral tegmental field (VTF) increased the level of extensor tone (Fig. 1, Fig. 2). Moreover, stimulation of the MLR region could interact with stimuli of the DTF or VTF by reducing or increasing the vigor of locomotion respectively. With paired stimulation of the MLR and DTF area, four-legged locomotion in the decerebrate cat was changed to locomotion of the hindlimbs only, and from hindlimb locomotion to total suppression of the ongoing stepping pattern with graded increases in the intensity of stimulation to the DTF (Mori et al., 1978). In contrast, simultaneous stimulation of the MLR and VTF region could change the pattern of locomotion from a walking to a galloping gait, depending on the activation level of the paired stimuli. Neuroanatomical and electrophysiological evidence have led to the identification of the DTF and VTF pathways.

Electrical stimulation of the DTF mainly activates fibers of passage originating from cholinergic neurons (Takakusaki et al., 1993) contained within the nucleus reticularis pontis oralis. These fibers project to the nucleus reticularis gigantocellularis that is contained within the MRF (Matsuyama et al., 1993, 1988; Iwakiri et al., 1994; Oka et al., 1993; Mori et al., 1992). Similar to previous studies on the initiation of locomotion (Noga et al., 1991), descending axons of neurons contained within the MRF descended within the VLF of the spinal cord before terminating in laminae VIII and VII (Matsuyama et al., 1988). The location of the VTF area corresponds to the rostral portion of the raphe nucleus (Mori et al., 1985) which is known to project descending axons through the VLF. Preliminary evidence suggests that the VTF receives inputs from the lateral hypothalamic area and the cuneiform nucleus (Mori and Ohta, 1986).

Mori and colleagues compared the responses obtained from decerebrate cats with similar activation of the DLF and VTF as well as the MLR and SLR in intact cats (Mori et al., 1989). Stimulation of the DLF in a cat that was freely moving would lead progressively to the cessation of walking followed by sitting and lying of the animal [Fig. 8(A)]. Conversely, stimulation of the VTF would cause a

---

Fig. 8. Effect of stimulating different locomotor regions in the intact freely moving cat (see text for more details). Abbreviations: DTF, dorsal tegmental field; VTF, ventral tegmental field; MLR, mesencephalic locomotor region; SLR, subthalamic locomotor region.
postural augmentation in a sitting cat followed by standing and spastic locomotion [Fig. 8(B)]. After stimulation of the MLR region, a cat would begin to walk or run without stopping, but it retained its ability to avoid obstacles [Fig. 8(C)]. If DLF stimulation was paired with the MLR stimulation in chronic cats, the postural support of the hindlimbs was suppressed and the cat stopped walking. Stimulation of the SLR region in the chronic cats also made a sitting cat locomote, but this time the movements, in contrast to VTF and MLR stimulation, were indistinguishable from normal movements [Fig. 8(D)]. It appeared that the animals adopted a searching type of behavior typical of normal cats. From these observations, Mori et al. (1992) suggested that the postural and locomotor synergies are structured in a hierarchy within the rostro-caudal axis of the brainstem, and that the command routing depends on interactions with the SLR, the MLR/PPN complex, the DTF and the VTF areas which are partly integrated at the MRF before continuing to the spinal cord.

2.8. Summary

The pathways that lead to the production of locomotion in the decerebrate cat have been parttraced. The MLR region of the brainstem receives inputs from the lateral segmental area of the hypothalamus, the basal ganglia and the limbic system. It is believed that these inputs lead to the production of different locomotor behaviors in the intact cat. A major pathway from the MLR continues to the MRF in the medulla. The MRF receives information from the forebrain, brainstem, cerebellum and from cutaneous afferents and is believed to be involved in the integration of posture and locomotion. The MRF can initiate and regulate the ongoing step cycle. Evidence from recent experiments suggests that one functional role for the MRF is the control of interlimb coordination. Although it is known that neurons from nuclei in the MRF project via the VL of the spinal cord and that they can have polysynaptic and monosynaptic connections with motoneurons in the spinal cord, it is not known how these projections can lead to the initiation of locomotion. However, a first step in realizing this goal has been the correlation of MLR stimulation with rhythmically active interneurons in the spinal cord. It has been shown recently that rhythmically active neurons that respond to stimuli delivered to the locomotor producing regions of the brainstem are located in laminae VII, VIII and around the central canal. Recent experiments using decerebrate cats have demonstrated that MLR-evoked walking can be blocked reversibly using NMDA antagonists, suggesting that glutaminergic and not monoaminergic drugs are essential for the development of a rhythmic motor pattern in the decerebrate cat. Areas that evoke postural changes accompanying locomotion have been identified in areas of the brainstem known as the DTF and VTF. It is thought that locomotor and postural control signals are integrated in the MRF and the spinal cord.

3. AFFERENT CONTROL OF LOCOMOTION

Indeed from the observations of Graham-Brown, an intrinsic automatic activity of the spinal centres seems the essential nervous mechanism responsible for stepping, a central activity comparable with that of the respiratory centre in the bulb, and like the latter, highly regulated by reflex action (Sherrington, 1924, as cited by Gossard and Hultborn, 1991).

3.1. Introduction

Animals rarely move about in an unchanging environment. Fish, for example, must be able to maneuver and change course in response to currents, vegetation and rocks. Terrestrial animals face far more variablity as they move across uneven terrain rife with its own dangers. To survive, animals must possess motor patterns that are robust yet flexible enough to handle unusual situations.

It is generally accepted that the basic rhythm-generating network is contained within the spinal cord and afferent input can access this circuitry and modify the ongoing pattern. An example of the power of afferent feedback can be observed when chronic cats with a transected spinal cord recover the ability to walk when trained daily on a treadmill (Barbeau and Rossignol, 1987). After 3 weeks, the cats can easily adjust their gait to the speed of the treadmill. Since these animals have a transected spinal cord, only afferent feedback from the moving limbs can provide the information necessary to adjust the output of the CPG. Another example which demonstrates the adaptability of the motor pattern by afferent feedback occurs when a split treadmill is used to drive each hindlimb of intact cats at different speeds. If one side is sped up in relation to the other, perfect coordination is maintained. The stance phase of the "fast" side is decreased relative to the "slow" side. These adjustments can be made not only in intact cats (Halbertsma, 1983) but also in decerebrate (Kulagin and Shik, 1970; Yanagihara et al., 1993) and low-spinal locomoting cats (Forsberg et al., 1980b).

During changes in gait it is the stance phase of the step cycle that is adjusted to the greatest degree. Consequently, when a cat speeds up, the length of the stance phase is reduced while the swing phase remains more or less the same (Grillner, 1981; Rossignol, 1996). From these observations, it was proposed that afferent feedback from a moving limb may control aspects of extensor muscle activity during the stance phase. Another possible role of afferent feedback is to gauge the amount of propulsive force that needs to be generated under different environmental conditions. For example, when a cat is walking uphill, the EMG amplitude of the extensors is increased compared to walking on a flat surface, while the flexor bursts remain unaltered (Pierotti et al., 1989). Recently, substantial progress has been made in identifying the types of afferents that contribute to the control of the duration and the amplitude of the
3.2. Reinforcement of the Ongoing Step Cycle

When an animal is walking, there must be a sufficient amount of tone in the extensor muscles to carry the weight of the animal. As mentioned previously (Section 2.7), before locomotion commences there is an increase in the level of postural tone in the extensor muscles which occurs by activation of descending pathways (Mori et al., 1992). Afferent feedback from extensor muscles adds to the maintenance of this postural tone and ensures that it is adjusted depending on the load carried by the limb. The concept that afferent feedback acts to reinforce activity in muscles has endured for over 30 years. For example, Yang et al. (1991) have estimated that 30–60% of the EMG amplitude in the soleus muscle may be accounted for by monosynaptic excitation of the motoneuron alone. Moreover, in the decerebrate locomoting cat, Severin (1970) estimated by reversible inactivation of the gamma motoneuron axons (thus eliminating the fusimotor drive to the extensor muscle spindles) that 50% of the extensor EMG activity was produced by group Ia activity. In addition to the monosynaptic pathway, a new oligosynaptic excitatory pathway has been discovered in the cat that is only open during locomotion and likely receives convergent afferent input from both groups Ia and Ib afferents (Figs 9 and 10) (Gossard et al., 1994; Pearson and Collins, 1993; Guertin et al., 1995a). The output from this pathway produces excitatory postsynaptic potentials (EPSP) in extensor motoneurons that are modulated in a phase-dependent manner. Studies from reduced preparations have demonstrated that input from extensor group I afferents that project onto this oligosynaptic pathway can reinforce the extensor burst. The following section will discuss the contribution from extensor group I afferents to the reinforcement of the extensor burst.

In the cat (Pearson and Collins, 1993), as in other species (DiCaprio and Clarac, 1981; Bässler, 1983, 1986; Lacquaniti et al., 1991; Skorupski, 1996; Skorupski and Sillar, 1986), there is a reflex reversal of the central effects of input from the force or stretch detecting afferents [Fig. 9(A)]. In the walking system of the cat, input from Golgi tendon organs (GTO) in extensor muscles onto extensor motoneurons is reversed from inhibitory to excitatory at the onset of locomotion (Pearson and Collins, 1993; Gossard et al., 1994). The pathway that has been used preferentially to show this effect is the one from plantaris (PI) to medial gastrocnemius (MG). This is because PI does not project any group Ia afferents directly to the MG motoneurons (Eccles et al., 1957b), thus all effects onto MG from PI are mediated by polysynaptic pathways. In the resting spinal cat, stimulation of the PI nerve at group I strengths results in the classic inhibition of the extensor burst [Fig. 9(A)] (originally described by Eccles et al., 1957a). However, when the locomotor CPG is activated (by adding clonidine) similar stimulation of the PI nerve during mid-stance results in an increase in the amplitude of the MG EMG [Fig. 9(A)]. It has been suggested that a locomotor-dependent oligosynaptic pathway that accesses the extensor half-center of the CPG is responsible for mediating this effect (Gossard et al., 1994); this is supported by studies which show that activation of group Iib afferents by stretching the triceps surae muscles can entrain and re-set the locomotor rhythm (Conway et al., 1987; Pearson et al., 1992). Recent evidence suggests that group Ia feedback from extensor muscles also can increase the amplitude of the extensor burst using the same oligosynaptic pathways as group Iib afferents (Guertin et al., 1995a).

Intracellular studies have complemented the above findings and have found that more than one excitatory group I pathway is opened during locomotion. The first oligosynaptic pathway has only been observed in fictively locomoting decerebrate cats (McCrea et al., 1995b). When extensor group I afferents are stimulated, a disynaptic EPSP can be observed in extensor motoneurons which is phasically modulated during the locomotor cycle. The functional role of this pathway is unknown, although it may provide more flexibility in the reinforcement of the extensor burst (McCrea et al., 1995a, 1995b), since it is hypothesized that this pathway lies outside the CPG. The second oligosynaptic pathway is opened after the administration of L-DOPA in spinal cats [Fig. 10(A)] or during MLR-ekvoked locomotion in decerebrate cats [Fig. 10(B)] (Gossard et al., 1994). Before L-DOPA is injected into an acute spinal cat, stimulation of group I extensor afferents [stimulus trains: 300 Hz (3–10 pulses)] causes summing IPSPs in the lateral gastrocnemius and soleus (LGS) motoneuron. When L-DOPA was added, the IPSPs were reduced gradually in size and replaced by slow rising EPSPs that, after 30 min, were large enough to cause a cell to fire an action potential. The MLR stimulation was equally effective in opening up this long-latency excitatory pathway. It is likely that the oligosynaptic pathway accesses the extensor half-center (CPG) since: (1) similar feedback that elicits this slow potential can entrain and reset the locomotor rhythm (Conway et al., 1987; Pearson et al., 1992); (2) the group I feedback can interact with the FRA system that is hypothesized to share circuitry with the half-centers (see Lundberg, 1981 for a review); and (3) extracellular recordings from rhythmically active candidate interneurons illustrate that contralateral FRA stimulation can increase the firing rate and can augment the excitation produced by ipsilateral group I excitation (Gossard et al., 1994). Furthermore, these interneurons are located in lamina VII, an area that contains interneurons that are rhythmically active in response to MLR stimulation (Noga et al., 1995a).

An important question is whether these findings are functionally relevant in the intact animal. Unfortunately, there are no studies in intact cats that have specifically tested whether stimulation of group I afferents can affect the amplitude of the extensor EMG burst. However, a study by Whelan et al. (1995a) found that in decerebrate walking cats, stimulation of the extensor group I afferents during stance tended to increase the amplitude of the extensor burst especially during late stance [Fig. 11(A)]. This suggests that extensor group I
Fig. 9. (A) Reinforcement of the ongoing extensor burst in the acute spinal cat. The schematic figure on the left shows the methods used to show group Ib reflex reversal in the cat. Under quiescent conditions, stimulation of the plantaris nerve would result in the classic Ib inhibition (Eccles et al., 1957a); however, under rhythmic conditions, group I input would cause a significant excitation of the MG EMG at a latency of 30-40 msec. Note that, since there are no monosynaptic inputs from PL to MG (Eccles et al., 1957b), all the observed effects were mediated by polysynaptic group I pathways (figures courtesy of Dr K. Pearson). (B) A schematic which represents the ensemble mean afferent firing rates from groups Ia, Ib and II muscle afferents located in the triceps surae muscles of freely stepping cats. Note that the mean firing rate of group Ib afferents follows the gastrocnemius EMG during the stance phase. Figure reproduced from Procházka et al. (1989), with permission.

Feedback is functionally relevant when the animal is receiving full afferent feedback from the stepping limbs. Afferent reinforcement of stance would be expected to be especially useful during mid-stance (E₂ phase) when the extensor muscles are stretched as the weight of the animal is partly borne by the limb. Presumably, the positive feedback from the increased firing of GTO afferents combined with negative
feedback from spindle afferents would act to resist this E$_l$ stretch. Recent modeling studies have supported the idea that positive feedback can act in this manner (Prochazka, 1996). Another proposal is that the reduction in positive feedback from extensor group Ib afferents at the end of stance allows swing to commence (Pearson, 1995a; Section 3.3.1).

Consistent with both of these proposals, ensemble recordings from both group Ib and Ia afferents in intact freely moving cats show that both have a high rate of firing during the stance phase [Fig. 9(B)] (Prochazka et al., 1989; Prochazka and Wand, 1980; Appenteng and Prochazka, 1984). For example, the ensemble firing rate of group Ib afferents from the

Fig. 10. (A) Excitatory actions of group I volleys recorded intracellularly in a LGS motoneuron after stimulating the PL nerve at 1.4 x $T$. Before the injection of l-DOPA and nialamide, stimulation of the PL nerve produced a small EPSP which was predominated by summating IPSPs which contribute to the classic non-reciprocal inhibition produced by the group Ib afferents. After treatment with l-DOPA and nialamide, the IPSPs were inhibited and is replaced by a slow rising EPSP that increases progressively in size as the locomotor pathway opens. (B) This trace shows the emergence of the group I excitatory response before and after stimulation of the MLR region in a paralyzed cat. (A) From top to bottom: tilted vertically are the high-gain intracellular responses (100 msec sweeps) to group I stimulation of the PL nerve (2 x $T$). Note that the first trace in this sequence shows the classic Ib inhibition, but the third trace in the sequence with MLR stimulation shows an excitatory response. The Em trace indicates the slow low gain intracellular record which indicates the locomotor drive potential. The last two traces are ENG traces from the tibialis anterior (TA) and the triceps surae (GS) respectively. Modified from Gossard et al. (1994), with permission. Abbreviation: PL, plantaris.
triceps surae muscles follows the activity of the gastrocnemius EMG with the highest firing rate occurring when the leg is loaded maximally during mid-stance [Fig. 9(B)]. Group Ia afferents from the triceps surae also fire at an appreciable rate during the stance phase (Prochazka et al., 1989; for review of spindle function see Hulliger (1984); Gladden (1992)). These results demonstrate that extensor group I afferents are active during stance in the intact cat and could participate in the reinforcement of stance.

3.3. The Control of the Stance to Swing Transition

Sensory feedback from the hindlimb can influence aspects of a cat’s locomotor pattern during walking. When a cat speeds up or slows down, adjustments are made to the length of the extensor burst, while the flexor burst remains unaltered. This adaptation is caused by afferent signals that regulate the transition from the stance to the swing phase. At the present time there are two proposals regarding the afferent control of the timing of the stance to swing transition during stepping. The first proposal is that a reduction in force feedback, due to the unloading of the extensor muscles at the end of stance, is the signal for initiating the transition from the stance to swing phase. This idea was advanced by Duysens and Pearson (1980) to explain the observation that stretches of the extensor muscles in decerebrate cats walking on a treadmill could inhibit the generation of the flexor bursts. The generation of the flexor burst was conditional on the force level being reduced below a level of 40 N. This led to the proposal that signals generated by the GTO and carried by Ib afferents could prolong the stance phase. The second proposal is that afferents from the hip signal the end of the stance phase when the hip angle extends past 95°. Grillner and Rossignol (1978) found that if a cat’s hindlimb was extended past 95°, flexion was induced, but if the limb was kept in a flexed position, tonic extension occurred. This section addresses the recent advancements that have supported these proposals. Although the two proposals are addressed separately in this review, it is quite likely that a combination of afferents signaling both load and leg position forms the basis for the transition from stance to swing.

3.3.1. Extensor Muscle Afferents

Input from proprioceptors can reset or entrain the motor rhythm in many vertebrate and invertebrate species (Andersson and Grillner, 1983; Bässler, 1983,1986, 1987; Clarac and Chraehti, 1986; Zill, 1985; McClellan and Jang, 1993; Pearson et al., 1992; Conway et al., 1987; Kiehn et al., 1992; for a review, see Pearson, 1993). Similarly, in the cat, input from group I extensor afferents can reset and entrain the generation of the flexor ENG burst in fictively locomoting decerebrate cats (Guerin et al., 1995a). This has led to the suggestion that group Ia and Ib afferents likely converge onto the oligosynaptic pathway that is open during locomotion (Guerin et al., 1995a).

One important issue is whether or not the group I feedback contributes to the timing of the step cycle when an animal is receiving full afferent feedback. Recently, Whelan et al., 1995a) observed in premammillary decerebrate cats that were walking on a treadmill, that stimulation of the extensor group I afferents during stance can prolong the extensor phase of the step cycle as shown in Fig. 11. Moreover, similar stimulation applied during swing resets the step cycle to extension. While these results are useful, it will be interesting to look at the effects of group I input in intact cats. The only study that has looked at this issue was done by Duysens and Stein (1978), who stimulated the LGS nerve at group I strengths during the step cycle and noticed virtually no effect on the rhythm. However, it is likely that they underestimated the effects of group I stimulation because: (1) the stimulus train frequency was too low (Whelan et al., 1995a); and (2) they tested their cats typically 3–7 days after the surgery and the efficacy of the LGS declines during this period of time (Whelan et al., 1995b).

3.3.2. Flexor Muscle Afferents

If a limb of a chronically walking spinal cat is held in a flexed position, the rhythm in that limb stops, while the contralateral limb continues to step. If the hip is extended past an angle of 95°, stepping resumes with the initiation of swing (Grillner and Rossignol, 1978). Similar effects of hip position were found in the generation of the scratch reflex in decerebrate cats (Berkinblit et al., 1978; Deliagina et al., 1984). In contrast to stepping, however, flexion of the hip was necessary for scratching to occur. Studies by Andersson and Grillner (1981, 1983) showed that sinusoidal movements of the hips in fictively locomoting spinal cats were capable of entraining the locomotor rhythm. In these studies, most of the hindlimb was deafferented, leaving only hip joint afferents and the muscles around the hip intact. The specific afferents that could be modulating this effect were not identified, although the flexor muscle spindle afferents activated due to stretch of the hip (Prochazka et al., 1976, 1977) were suspected (cf. Kriellaars et al., 1994). Qualitatively similar results...
have been obtained in the forelimb. Retraction of the shoulder (which extends the flexors of the shoulder) increases the amplitude of the flexors and inhibits the activity in extensors (Rossignol et al., 1993).

Recently, Hiebert et al. (1996) have identified proprioceptive inputs from flexor muscles that can alter the timing of the step cycle in the hindlimb. To identify the afferents involved, Hiebert et al. (1996) stretched the iliopsoas, and/or tibialis anterior, and/or extensor digitorum longus muscles during the stance phase in spontaneously walking decerebrate cats [Fig. 12(A)]. Stretch of these flexor muscles inhibited the ongoing stance phase and promoted an earlier onset of flexion [Fig. 12(B)]. One conclusion from these data is that activation of muscle receptors in both the hip and the ankle have similar effects on shortening the stance phase and initiating swing. Another conclusion is that the length sensitive spindle afferents from flexor muscles in the hip and ankle affect the transition from stance to swing since vibration (EDL and/or IP) or electrical stimulation at group Ia strengths (EDL) or electrical stimulation at group II strengths (TA) each inhibit stance. However, contrary results have been obtained by Perreault et al. (1995). In this study, in which fictively locomoting decerebrate cats were used, stimulation of group II afferents reset the locomotor rhythm to extension. It is conceivable that the use of different preparations [spontaneously walking (Hiebert et al., 1996) vs fictively locomoting decerebrate cats (Perreault et al., 1995)] may explain why the results differed.

3.3.3. Cutaneous Afferents

Nearly a century ago, it was recognized that cutaneous stimulation of the distal foot could produce various excitatory extensor reflexes in animals at rest (extensor thrust: Sherrington, 1906; positive supporting reaction: Magnus, 1926; toe extensor reflex: Engberg, 1964), and hence it was hypothesized that cutaneous reflexes might serve to reinforce the stance phase during locomotion. Since that time, it has been shown that the extent to which cutaneous input affects the step cycle depends firstly on the phase of the step cycle that the perturbation...

Fig. 11. (A) Rectified and filtered EMG traces during spontaneous stepping of a premammillary cat on a treadmill. During mid-stance, a stimulus train applied to the LGS nerve (trains: 1.8 x T; 1000 msec duration; 150 Hz) extended the duration of the ipsilateral MG nerve and delayed the onset of the flexor burst. The contralateral leg indicated by the contralateral St continued to step normally Reproduced from Whelan et al., with permission. (B) Stick figures which show the movement of the limb (indicated by horizontal arrow) during the stance phase of normal walking (left trace) and a stimulated step (right trace). The heavy lines indicate when the stimulus to the LGS was applied and the arrow points to where flexion would have occurred normally without stimulation. (C) Kinematic information showing the excursion of the hip, knee and ankle joints during a normal step (thin line) and a stimulated step (thick line). Note that the hip, knee, and especially the ankle, joints remained in extension during the stimulus (black bar) and that flexion resumed after the stimulus offset (previously unpublished information). Abbreviations: LGS, lateral gastrocnemius-soleus; St, semitendinosus; Co, contralateral; I, ipsilateral; MG, medial gastrocnemius.
is delivered and secondly, on the strength and type of
stimulation (Duysens and Stein, 1978; Duysens, 1977;
Duysens and Pearson, 1976; Grillner and Rossignol,
1978; Forssberg, 1979). Activation of cutaneous
afferents can elicit complex patterns of behavior that
are functionally relevant to the animal. For example,
stimulation of cutaneous afferents from the dorsum
of the foot can evoke the well known stumbling
corrective response (Forssberg, 1979). This response
ensures that an exaggerated flexion response occurs if
a perturbation is encountered during the swing phase,
while in contrast if the perturbation is encountered
during stance the extensor burst is enhanced.
However, it is less known to what extent cutaneous
afferents control the stance to swing transition during
unperturbed locomotion.

When discussing this issue, it must be kept in mind
that cutaneous afferents can, in theory, signal length,
pressure (force), and velocity information during
walking as well as nociception depending on the type
Experiments in premammillary cats which have
electrically stimulated cutaneous afferents that
innervate areas of the skin which sense yield of
the ankle (sural) and innervate the foot-pad (posterior
tibial) have shown that stance can be prolonged and
enhanced (Duysens, 1977; Duysens and Pearson,
1976; Duysens and Stein, 1978). For example, weak
electrical stimulation of the sural nerve during late
flexion terminates flexion prematurely and resets the
rhythm to extension. In contrast, if the same stimulus
is applied during early flexion, the flexor bursts are
frequently augmented and the subsequent extensor
burst is shortened (Duysens, 1977). In many cases,
stimulation of the sural nerve during late stance
increases the duration and the amplitude of the
extensor burst by over 100% and completely
abolishes the ongoing ipsilateral flexor burst (Duy-
sens and Pearson, 1976). It is not known whether the
spinal circuitry mediating this effect shares common
interneurons with proprioceptive afferents from the
extensor and flexor muscles (Sections 3.3.1 and 3.3.2).

3.4. A Model Circuit

A scheme summarizing the inputs from the
proprioceptive and exteroceptive afferents is shown in
Fig. 13. It is assumed that the locomotor rhythm is
generated by mutually inhibiting half-centers (Lund-
berg, 1981; Jankowska et al., 1967a, 1967b). One of
the problems with the half-center model initially
proposed by Lundberg (1969) was that it predicted a
simple alternation between flexors and extensors
during walking. The complex activity of flexors and
extensors that is observed during walking (Engberg and Lundberg, 1969) was hypothesized initially to be due to afferent feedback which sculpted the simple rhythm produced by the half-center (Lundberg, 1969). This proposal was contradicted by experimental data obtained from postmamillary decerebrate cats that were walking on the treadmill which clearly showed that a complex pattern of muscle activity could be produced without afferent input (Grillner and Zangger, 1984). In light of this, the half-center model has been expanded by Perret (1983) to allow for a central oscillatory network (half-center model) that produces the general timing of the network and a system of premotoneuronal interneurons which sculpts the final output and produces the complex activation of extensor and flexor muscles that is observed during stepping [similar proposals have been made for the operation of the scratch reflex (Koshland and Smith, 1989), and for the respiratory system (Feldman, 1983)]. As a result, the half-center hypothesis remains a convenient model for discussing the actions of afferent feedback on the timing of the locomotor pattern. For the sake of simplicity the premotoneuronal network proposed by Perret (1983) is not indicated in Fig. 13. In this model, it is assumed that both extensor and flexor afferents project onto the extensor half-center and affect the timing and the amplitude of the extensor burst (pathways 4 and 5 in Fig. 13). Afferent input from group I extensor afferents also affects the amplitude of the extensor burst by acting on the premotoneuronal network that lies outside the CPG (McCrea et al., 1995b; pathway 3 in Fig. 13).

During locomotion, group I afferent feedback from the extensors causes both an excitation of the extensor burst and an alteration in the timing of the step cycle. Due to the long latency of the EPSP in extensor motoneurons when group I extensor afferents are stimulated, the pathway is likely to be polysynaptic. This pathway receives convergent afferent information from many different extensor muscles (Whelan et al., 1995a; however, see Gossard et al., 1994) and globally excites the extensor muscles in the ipsilateral limb by an excitatory action on the extensor half-center (Guertin et al., 1995a). Group Ia feedback from muscle spindle afferents also excites the extensor half-center (Guertin et al., 1995a) as well as directly exciting extensor motoneurons (pathway 1 in Fig. 13). Thus, combined activity from group Ia and Ib afferents located in extensor muscles tends to prolong the extensor burst and prevent premature flexion of the limb while the limb is loaded.

The flexor muscle spindle afferents inhibit the extensor half-center (pathway 5 in Fig. 13) and thus act to curtail the extensor burst and cause the onset of the swing phase (Hiebert et al., 1996). In theory,
there are two possibilities by which the flexor muscle afferents could affect the timing of the step cycle: (1) the flexor muscle afferents could directly activate the flexor half-center and inhibit extensor activity by the resultant inhibition of the extensor half-center; or (2) the flexor afferents could activate the flexor half-center by inhibiting the activity of the active extensor half-center. Although both are plausible, evidence favors the latter possibility. This assertion is based on two pieces of evidence: (1) the latency for inhibition to occur in the extensor muscles is extremely rapid (30 msec) and is similar to that reported for extensor afferents while in contrast (2) the minimum latency for the initiation of flexor activity was 90 msec, indicating that the extensor half-center is inhibited before the flexor half-center (Hiebert et al., 1996). The stance to swing transition is likely to be signaled by a combination of a reduction in extensor afferent feedback due to the unloading of the limb combined with an inhibition of the extensor half-center by flexor muscle afferents as the leg is extended and the flexor muscles are stretched. However, it is clear that during stimulation of the LGN grow I afferents the leg is powerfully extended (Fig. 11(C); Whelan et al., 1995a). In this case, it is clear that signals from the flexor muscle afferents that are stretched cannot overcome this powerful extension. This may be functionally relevant as the maintenance of ground support is critical when extensor muscles are loaded and under these conditions feedback from flexor muscle afferents may be less effective.

A contribution from certain low-threshold cutaneous afferents such as those within the sural nerve (Duyssens and Pearson, 1976; Duyssens, 1977; Duyssens and Stein, 1978) is likely to contribute to the excitation of the extensor half-center, as indicated by the dotted line in Fig. 13. While it is assumed in this model, for the sake of simplicity, that many of the effects on the step cycle from groups of afferents excite or inhibit interneurons that comprise the extensor half-center, it is entirely possible that these afferents may also project onto the flexor half-center. For example, in fictively locomoting decerebrate cats, resetting of the locomotor rhythm by stimulation of the group I extensor afferents during the flexor phase of the locomotor cycle is accompanied by a simultaneous excitation of the extensor motoneurons and by an inhibition of the flexor motoneurons (Guertin et al., 1995b). These results suggest a more global regulation of the central pattern generator, rather than a selective input to the extensor half-center.

3.5. Summary

In the intact and the reduced animal, changes in cadence are mainly due to an alteration of the stance and not the swing phase. This finding led to the assumption that the afferent control of the step cycle is directed at modulating the duration and amplitude of the extensor burst. The transition from stance to swing is a point in the step cycle that appears to be especially susceptible to afferent control. Thus the CPG can be accessed by signals from extensor and flexor muscle afferents that can powerfully alter the duration of stance and reset the step cycle (Whelan et al., 1995a; Hiebert et al., 1996; Conway et al., 1987; Pearson et al., 1992). It is hypothesized that the signal for the end of stance is conveyed by afferent feedback in two ways to the CPG: (1) unloading of the limb causes a reduction in the positive feedback from the group Ib extensor muscle afferents onto the extensor half-center; and (2) increased inhibition of the extensor half-center by inputs from the flexor muscle afferents which are lengthened throughout the stance phase of the step cycle. It must be kept in mind that the motor control system is multisensorial and is likely to be highly redundant. Information concerning the appropriate rhythm to adopt comes from the activity of afferents in all the stepping limbs including the forelimbs and by the descending drive onto the spinal CPG, as well as any modulation from other descending inputs. In light of this, the inputs from the proprioceptors should be considered in global terms (Pearson and Ramirez, 1996). Indeed, it would be very surprising to find that the nervous system relies on only one single modality to calibrate motor programs considering the amount of convergence of different afferent groups onto interneurons in the spinal cord (Baldissera et al., 1981; Harrison et al., 1983; Jankowska, 1992; Jankowska and McCrea, 1983; Jankowska et al., 1981).

4. PLASTICITY OF LOCOMOTOR PATHWAYS INVOLVED IN THE PRODUCTION OF LOCOMOTION

Complex motor patterns such as the playing of a Beethoven piano sonata or the fielding and throwing of a baseball are not executed correctly on the first attempt. Rather, initial efforts are corrected, refined and finally perfected by a process that involves making errors, detecting them through sensory inputs and correcting the errors on subsequent repetitions of the movement. The process that improves motor performance through practice is called motor learning (Lisberger, 1988).

The ability of animals to learn a new behavior is an essential component of the developmental process and is critical for their survival. Many examples of adaptation in general are known in neurophysiology, including the re-mapping of the auditory system in the barn owl (Knudsen and Knudsen, 1990), the adaptation of the vestibulo-ocular reflex (Lisberger, 1988), chronic spinal cats can regain their ability to walk following regular training (Barbeau and Rossignol, 1994, 1987; Barbeau et al., 1993; Barbeau and Blunt, 1991; Edgerton et al., 1992; Lovely et al., 1986) and the re-mapping of the spinal cord sensory map after injury (Devor and Wall, 1978). However, relatively little is known about how locomotor systems adapt in response to new environmental conditions or injury. Recently, plasticity has been found to occur in an afferent pathway that is functionally important in the control of the stance to swing transition (Whelan et al., 1995b) after partial axotomy of the extensor afferents. The recalibration
of the afferent pathway occurs in a manner that is beneficial to the animal and may be related to the recovery of function after the injury. Another recent development is the demonstration that decerebrate cats (Yanagihara et al., 1993) and ferrets (Lou and Bloedel, 1988; Bloedel et al., 1987; Bloedel et al., 1991) can quickly learn new locomotor behaviors. These studies open the door for an investigation into the areas of the brainstem and spinal cord that could be involved in the adaptive modification of motor tasks. These studies are among the first to concentrate on functional plasticity in decerebrate animals.

4.1. The Ability of the Decerebrate Animal to Learn New Behaviors

It has been known for quite some time that the decerebrate animal can learn new patterns of behavior. For example, the eye-blink response can be classically conditioned in the decerebrate cat by using auditory discriminating stimuli (Norman et al., 1977). The flexor withdrawal reflex can be classically conditioned in both the decerebrate dog (Bromiley, 1948) and the spinal cat (Patterson et al., 1973). However, until recently it was not known whether a decerebrate animal could alter a behavior in a functionally relevant manner while walking.

Yanagihara et al. (1993) found that chronic decerebrate cats can adapt their interlimb coordination appropriately when their limbs are driven at different velocities relative to each other. Animals were mounted over a treadmill, which allowed the left forelimb of the animals to be driven at different velocities. When the left forelimb was driven at twice the velocity of the other three limbs, there was an immediate disruption of the stance phase of the left forelimb. However, within 50 steps the step cycle of the left (and right) forelimb stabilized. Subsequent perturbations showed an immediate adaptation indicating that the decerebrate animal had some "memory" of the perturbation. Recently, Lou and Bloedel (1988) have shown that the trajectory of a forelimb in decerebrate locomoting ferrets can be conditioned to avoid an obstacle. What is quite surprising [Fig. 14(A)] is that the new behavior is learned within 5–15 trials, and moreover the behavior can be eliminated after a number of trials if the bar is removed. The authors later combined recordings from Purkinje cells [Fig. 14(B)] and monitored both simple and complex spikes during perturbed and unperturbed walking (Lou and Bloedel, 1992). During unperturbed walking, the complex spike activity was not correlated with the step cycle. When the bar was introduced, the production of the complex spikes became highly correlated to the perturbation. Studies by Yanagihara and Udo (1994) confirmed that in the decerebrate locomoting cat similar perturbations of the forelimb lead to synchronization of the complex spikes (cf Matsukawa and Udo, 1985) and to an altered firing of the left and right Deiter's nucleus (Udo et al., 1982). Bloedel (1992) has hypothesized that synchronization of climbing fiber input activates sagittally aligned Purkinje cells and causes an on-line change in the efficacy of mossy fiber inputs. This would lead to an alteration in the output of cerebellar nuclear neurons every time the perturbation is encountered by the animal. Thus, instead of the cerebellum being involved in the teaching of the new behavior, it is a part of the circuit that controls the new behavior (Bloedel, 1992; Bloedel and Ebner, 1985). Consistent with this idea, preliminary evidence suggests that ablation of areas of the cerebellum does not abolish the acquisition of the bar avoidance task in decerebrate ferrets (Bloedel et al., 1987; Bloedel et al., 1991), although it does alter the performance of the movement.

It is not known whether the site of plasticity for all the behaviors discussed above is located in the brainstem or cervical spinal cord. It is possible that the site of plasticity may not be located within a defined area and may be distributed in the spinal cord and brainstem (Bloedel and Bracha, 1995; Dr James Bloedel, personal communication).

4.2. Plasticity of the Extensor Group I Pathway

Plasticity of reflex pathways can occur in response to muscle inactivity, axotomy of peripheral nerves, conduction block of afferent activity, and operant conditioning (for a review, see Mendell, 1984; Mendell, 1988; Wolpaw and Carp, 1993). Most studies on reflex pathways have concentrated on the adaptation of the monosynaptic group Ia pathway due to its relative simplicity. In contrast, research on plasticity within polysynaptic pathways is not as well established. Recently, it has been found that a polysynaptic pathway that functionally regulates the timing and reinforcement of the stance phase can be recalibrated in a functionally relevant manner (Whelan et al., 1995b). It was found that the strength of this polysynaptic reflex can be altered if the load on an extensor muscle is increased by cutting the nerve supplying a synergistic extensor muscle (Whelan et al., 1995b). In this study, the left LGS nerve was cut in intact cats, resulting in increased loading of the intact MG muscle. After recovering from this minor surgical procedure, the cats typically showed a yield in the ankle during the stance phase which returned to normal in a period of one week (cf Wetzel et al., 1973). To test whether adaptation had occurred in the group I excitatory pathways, the cats in the study were decerebrated at various times after the initial cut of the LGS nerve (3–28 days) and implanted with small neural stimulating cuffs around the LGS and MG nerves in both the operated and control hindlimbs. During stepping, each extensor nerve was stimulated separately during stance using long stimulus trains (1000 msec train; 200 Hz stimulation at 1.8 × T and 0.2 msec pulse width). As expected in the control limb, stimulation of the LGS nerve extended the duration of the stance phase for the duration of the stimulus [Fig. 15(C)] (Whelan et al., 1995a), while stimulation of the synergistic MG nerve extended the duration of stance relatively weakly [Fig. 15(A)]. The situation in the experimental limb was quite different. Starting as soon as three days after the axotomy of the LGS nerve, stimulation of the MG nerve could powerfully prolong stance [Fig. 15(B)], while in contrast, the previously cut LGS nerve typically only weakly prolonged the stance phase [Fig. 15(D)]. The time course of this effect was
not addressed in this study, although it was noted that declines in LGS and increases in MG efficacy can occur as early as 3 days after the initial cut (Fig. 15(E) and (F)).

There are two main differences between the changes that presumably occur in the oligosynaptic pathway and those that occur at the monosynaptic junction. Firstly, the time course for the changes in reflex efficacy is much faster than those observed for the monosynaptic reflex (for a review, see Mendell, 1984), in which the Ia EPSP evoked from the cut extensor nerve does not decrease until at least 7 days after the axotomy (Eccles et al., 1959; Eccles and McIntyre, 1953). Secondly, although some researchers have reported that the monosynaptic reflex from synergists can increase after axotomy (Eccles et al., 1962; cf Decima and Morales, 1983), other researchers have failed to replicate this result (Walsh et al., 1978; Gallego et al., 1979). In contrast, the oligosynaptic response from the synergists increased predictably and quickly (within 5 days) (Whelan et al., 1995b). Accordingly, whatever the system responsible for the plasticity in the locomotor dependent group I pathway, it is likely different than the mechanisms that alter the strength at the monosynaptic connection between the Ia afferents and motoneurons upon axotomy of extensor nerves.

At present, there are a number of unresolved issues regarding the development of the plasticity within the group I oligosynaptic pathway: (1) the site of plasticity has not been determined; (2) if the site of plasticity is contained within the spinal cord it would be interesting to know whether the neural circuitry within the spinal cord can reconfigure in isolation or whether supraspinal descending commands from the...
Control of Locomotion

Fig. 15. (A), (B), (D) and (E) rectified and filtered EMG traces from a decerebrate walking cat that had its LGS nerve axotomized 21 days prior to the acute experiment. During late stance, an extensor nerve was stimulated (2 × T; 1000 msec duration; 200 Hz). (A) Stimulation of the control MG nerve (A) weakly extended the VL extensor burst whereas, in the experimental limb (B), a similar stimulus powerfully prolonged stance for the duration of the stimulus train. In contrast to MG, stimulation of the LGS in the control leg powerfully prolonged stance (D) whereas, in the experimental leg (E), a similar stimulus applied to the previously cut LGS nerve resulted in a small effect on the duration of the extensor burst. (C) and (F). These bar graphs show the average effects of the experimental and control LGS and MG nerves for each experiment and are compiled from 13 experiments that were performed 2–28 days after axotomy of the LGS nerve. Each bar represents the average percentage effectiveness of the stimulus burst in enhancing the extensor burst during a single experiment, which is calculated by the following equation:

% effectiveness = [(b – a)/(c – a)] × 100. The error bars represent the S.D. Modified from Whelan et al., 1995b, with permission. Abbreviations: LGS, lateral gastrocnemius-soleus; MG, medial gastrocnemius.

cerebellum, for example are necessary; (3) intracellular recordings similar to those of Gossard et al. (1994) will have to be performed to confirm the hypothesis formed by Whelan et al., 1995b) that the oligosynaptic pathway outlined by Gossard et al., 1994) is indeed changing in strength independently of the group Ia monosynaptic pathway; and (4) the possibility that the recovery of function of the animal after the cutting of LGS is correlated to the plasticity that has been observed by Whelan et al., 1995b) needs to be explored.

4.3. Summary

Plasticity of neural structures is only beginning to be understood. Mammals can still show complex adaptive behavior after decerebration illustrating that, even in these reduced preparations, functionally relevant adaptation can take place. Decerebrate ferrets, for example, can learn a new trajectory of locomotion if a bar is placed in the path of the moving leg (Lou and Bloedel, 1988, 1992). These new behaviors can be produced after as little as from five to ten presentations of the bar. It is unknown which structures in the brainstem could be controlling the change in trajectory. Plasticity of the group I oligosynaptic pathway that occurs after chronic axotomy can be retained after decerebration (Whelan et al., 1995b), indicating that the site of plasticity is
contained within an area caudal to the premammillary transection.

5. CONCLUDING REMARKS

And if they with their knowledge and the means at their command often seemed to walk haltingly or even to have gone astray, we may ask ourselves this question: Are not we, with all the knowledge and the means at our command, walking also haltingly...? Shall we not seem to those who tell our story a hundred years to come? For indeed it is one of the lessons of the history of science that each age steps on the shoulders of the ages which have gone before.

(Foster, 1901, p. 299).

Watching a decerebrate cat walk is a remarkable experience*. At times the walking pattern is similar to that of an intact animal with perfect interlimb coordination and weight support. The ability to generate locomotion is a result of interactions between the descending command signals from the brainstem, the CPG in the spinal cord and afferent feedback. This mutual dependence among structures is one of the common principles in the generation of locomotion. For example, stimulation of the MRF can cause changes in the amplitude of all four limbs in the cat in a phase-dependent fashion during locomotion, suggesting that the descending signals are optimized by the CPG (Drew and Rossignol, 1984). Other brainstem areas reinforce activity during locomotion, such as Deiter’s nucleus that affects the anti-gravity muscles (Orlovsky, 1972a), and the red nucleus which affects the flexor portion of the step cycle (Orlovsky, 1972a). The phasic pattern of the brainstem nuclei is in turn dependent on feedback from the CPG arriving via the VSCT (Arshavsky et al., 1972a, 1972b, 1972c; Arshavsky et al., 1986; Orlovsky, 1970; Orlovsky, 1972b, 1972c). The cerebellum filters the ascending information from the VSCT and outputs a phasic signal to Deiter’s nucleus, the MRF, and the red nucleus (Arshavsky et al., 1986; Arshavsky and Orlovsky, 1986). In addition to feedback from the CPG, the MRF region also receives direct input from afferents in the limbs and in turn outputs signals that reinforce activity in flexor motoneurons (Shimamura et al., 1990). Besides reinforcing the activity of neurons in the brainstem, afferent input from the hindlimb potently affects the stance to swing transition in the cat. Thus the rhythm generated by the CPG can be altered and molded by afferent feedback to reflect variations in the terrain.

Another common principle in the control of locomotion is that the connections between and within structures involved in controlling locomotion are extremely flexible. It is this flexibility that ensures that appropriate responses can be made to an ever changing environment. For example, when locomotion is initiated in the decerebrate cat, there is a state change that causes many systems in the brainstem and spinal cord to be optimized for the task at hand. To cite an instance, many neurons within the brainstem MRF alter their response characteristics during locomotion so that cutaneous input is gated out during phases of the step cycle when the cells are inactive. Gating of afferent inputs occurs at the segmental level within the spinal cord during locomotion. Phasic presynaptic inhibition of cutaneous (Gossard et al., 1990) and proprioceptive afferents (Baev and Kostyuk, 1982) ensure that afferent input can only affect the locomotor rhythm when appropriate. More radically, the actions of some reflex pathways are fully reversed when locomotion commences. A case in point is the reflex reversal that occurs in the reflex pathway from Golgi tendon organs. At rest, afferent input from extensor GTOs inhibit the extensor burst, but during locomotion similar stimuli reinforce the extensor burst. Thus, throughout the neuraxis, locomotor pathways are not hard-wired and can be flexibly rewired depending on the “state” of the animal (see Prochazka, 1989, for a review of this issue).

In conclusion, the decerebrate cat can produce a locomotor pattern that is dependent on its “state” and the mutual interdependence of all the structures present. But how does the locomotor performance of the decerebrate cat compare with the intact animal? The intact cat is capable of a large amount of motor behaviors. For example, as I am writing this review, my pet cat is waiting for his ball to be thrown, an activity that gives him a great deal of pleasure. When I throw the ball around the corner, he leaps out of my lap and gallops after the ball and often catches it in mid-air. He then turns around, slowly walks back to me, and drops the ball into my lap so that I can throw it again. If we look at this behavior from the perspective of this review this activity is breathtakingly complex. In response to a visual stimulus (the ball), a command signal is initiated in the cortex that is presumably sent to the MLR and MRF to initiate a galloping pattern. When the animal turns the corner, the interlimb coordination has to be adjusted so that the outer limb cycles at a slower rate than the inner limb. Finally, the animal has to superimpose a jumping behavior on top of the preexisting galloping pattern. To make the jump, the animal has to take into account the velocity of the ball relative to its own and judge the necessary acceleration necessary to catch it. Research into understanding how complex locomotor behaviors, like the one described, are initiated and controlled, is at an early stage, but some principles are emerging. For example, when a cat is locomoting in a predictable environment it appears that much of the locomotor pattern is produced by “lower” structures such as the brainstem and spinal cord (Belozerova and Sirota, 1993; Drew, 1988, 1991 Armstrong, 1988). This is equivalent to my cat’s slow walk after catching the ball. However, if an animal unexpectedly encounters an obstacle, neurons in the motor cortex are activated that may be involved in adjusting the pattern in both the fore and

*A copy of a film that was made by Graham-Brown in 1939 that demonstrates the ability of decerebrate cats to locomote on a treadmill is available from the British Medical Association (Armstrong, 1986). Copies for purchase can be obtained by writing to: BMA/BLAT Film Library, BLAT Centre, BMA House, Tavistock Square, London, WC1H 9JP, U.K.
hindlimbs so that the limbs clear the obstacle (Drew, 1993; Widajewicz et al., 1994; cf Marple-Horvat et al., 1993; Prentice and Drew, 1995). Recordings thus far have only been made from cells in the motor cortex and cerebellum because of the few researchers undertaking this research and the technical challenges involved. It is clear that, despite the technical challenges of performing experiments on conscious animals, this may be the only way to understand how all areas of the locomotor system are incorporated into the goals of the animal.

Acknowledgements—I would like to thank Dr K. Pearson for many worthwhile discussions concerning previous drafts of this manuscript. I would also like to thank Dr R. B. Stein and G. Hiebert for reading the manuscript and offering suggestions for its improvement. This work has been supported in part by the Alberta Heritage Foundation for Medical Research, the Natural Sciences and Engineering Council of Canada and the Medical Research Council of Canada.

REFERENCES


Brudzynski, S. M., Houghton, P., Brownlee, R. D. and Mogenson, G. J. (1966) Involvement of neuronal cell bodies of the


Marilinski, V. V. and Voitenko, L. P. (1992) Participation of the medullary reticulotegmental formation of the medulla oblongata in the


