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Locomotor capacities after complete and partial lesions of the spinal cord

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Abstract. This paper first reviews some of the observations made on the locomotor capabilities of several animal species with a special emphasis on cats and including primates and man after complete spinal lesions. We show that animals can perform well-coordinated walking movements of the hindlimbs when they are placed on a treadmill belt and that this locomotion is also adaptable to speed and perturbations. Cats with partial spinal lesions of the ventral and ventrolateral parts of the cord can perform voluntary quadrupedal locomotion overground or on the treadmill albeit with deficits in weight support and interlimb coordination. We also show that some drugs such as clonidine (an alpha-2 noradrenergic agonist) can be used to trigger locomotion in early-spinal cats and discuss the effects of various neurotransmitter systems on the expression of the locomotor pattern in both complete and partial spinal cats. It is concluded that a pharmacological approach could be used, in combination with other approaches, such as locomotor training and functional electrical stimulation, to improve locomotor functions after spinal cord injuries in humans.

Review

Key words: locomotion, spinal cord, spinal pathways, interlimb coordination, locomor pharmacology, clonidine, partial spinal lesions

INTRODUCTION

Information on the locomotor capabilities of animals subjected to spinal lesions is of great interest in the context of gait rehabilitation of patients with spinal cord injuries (Barbeau and Rossignol 1994). This knowledge can be very helpful in orienting the study of patients as well as in the design of rehabilitation approaches (Rossignol and Barbeau 1995). In the first section of this paper, we will summarize some observations obtained on the locomotor abilities of cats with complete spinal transection at T13 and also introduce more recent work on cats with partial ventral and ventrolateral lesions of the cord at the same level. In a second section we will briefly discuss the effects of agonists and antagonists of different neurotransmitter systems in cats with total or partial spinal lesions. This is aimed at better understanding how the activation or blockade of different receptors of these neurotransmitters could participate in various aspects of the control of locomotion such as its initiation and the modulation of its timing and amplitude characteristics and how they could be used to improve gait rehabilitation in patients. For some general background on locomotor mechanisms, several reviews can be helpful (Grillner 1981, Armstrong 1986, Grillner and Dubuc 1988, Pearson 1993, Rossignol and Dubuc 1994, Rossignol 1996).

LOCOMOTOR CAPABILITIES OF ANIMALS WITH SPINAL LESIONS

Complete spinal lesion

HISTORICAL PERSPECTIVE AND GENERAL DESCRIPTION

At the turn of the century, it was shown that, one or two days after a spinal section, cats and dogs can perform spinal standing (dogs better than cat because more weight is supported by forelimbs). Sherrington (1899, 1910a,b) described the locomotion of spinal animals (dogs and cats) as "the postural act of standing upon which there are grafted rhythmic flexion-extension movements of each limb in turn, resulting in locomotion". In the decapitated cat (high spinal), he showed that stimulation of the perineum or a foot or "faradization" of an afferent nerve can elicit stepping, as well as the stimulation of the cut end of the bulb or spinal cord which can evoke mainly unilateral stepping on the stimulated side. Sherrington writes that "the rhythmic response of the musculature is referable to a rhythm not resident in the stimulus or in sense-organs of the skin, but developed in the spinal centres occupied with the reflex action. In other words, in these centres there arises a rhythmically recurrent refractory phase... Indeed, the burden of shunting from flexion to extension and vice versa is thrown greatly upon mechanisms wholly intrinsic to the cord (Sherrington 1910b). This is already a clear statement on the generation of locomotion within the spinal cord, a view strongly defended by Brown (1911) an thoroughly reviewed elsewhere (Grillner 1981, Rossignol 1996).

Since these celebrated accounts on reflexes, walking and standing in spinal animals, there have been several reports on the reflex and motor capabilities of animals with a complete transection of the spinal cord. Table I lists some key references on locomotor functions after chronic lesions made at various levels in different animal species and at various ages. The following description summarizes some aspects only of this topic.

After a spinal transection, dogs were shown to eventually redress voluntarily by supporting their weight on the forelimbs and lifting their hindquarters (Philippson 1905, Ten Cate 1939, Kellogg et al. 1946). These movements were reported to be better when the animal was allowed to move every day for a few hours (similar results have been reported recently on walking and air stepping in chronic adult spinal dogs; Naito and Shimizu 1991, Shimizu 1991). Spontaneous walking for long distances on all 4 limbs could be performed even after a second transection (see however Sherrington 1899). Shurrager and Dykman (1951) reported observations in kittens spinalised at the age 2 days to 12 weeks and 1 dog. In both the cats and dog, they reported unaided

TABLE I

List of references related to locomotor studies after complete spinal lesions at different levels at various species. For man, anatomically complete refers to surgical or to Magnetic Resonance Imaging confirmation of the completeness of the lesion

Chronic complete spinal section in different species

Species	Level of transection	References
MAN	Anatomically complete at various levels	(Holmes 1915, Kuhn 1950, Dietz et al. 1994, Dietz et al. 1995)
MONKEYS	thoracic (undefined)	(Philippson 1905, Freeman 1952)
MONKEYS	Th 6-9	(Eidelberg et al. 1981b, Eidelberg 1983, Vilensky et al. 1992)
DOGS-pups		(Freeman 1952)
DOGS-adults	6-10 thoracic	(Sherrington 1899, Philippson 1905, Sherrington 1910b, McCouch 1947, Shimizu 1991)
DOG-adults	L1-L3 + S2-S3 for (Ten Cate, 1939)	(Ten Cate 1939, Kellogg et al. 1946, Shurrager and Dykman 1951, Naito et al. 1990, Shimizu 1991)
CAT-Kittens and infants	Th12 to L1 and L3	(Shurrager and Dykman 1951, Freeman 1952, Forssberg et al. 1980a, Forssberg et al. 1980b, Smith et al. 1982, Goldberger 1986, Robinson and Goldberger 1986b)
CAT-ADULT	C1	(Miller and Van der Meche 1976, Zangger 1981)
CAT-ADULT	Th 3-4	(Ranson and Hinsey 1930, Kozak and Westerman 1966)
CAT-ADULT	Th 6-10	(Ranson and Hinsey 1930, McCouch 1947, Eidelberg et al. 1980)
CAT-ADULT	Th13-L1	(Sherrington 1910a, Ranson and Hinsey 1930, Ten Cate 1962, Kozak and Westerman 1966, Afelt 1970, Baker et al. 1984, Goldberger 1986, Lovely et al. 1986, Robinson and Goldberger 1986a,b, Barbeau and Rossignol 1987, Barbeau et al. 1987, Giuliani and Smith 1987, Rossignol et al. 1989b, Lovely et al. 1990, Barbeau and Rossignol 1991, Edgerton et al. 1991, Roy et al. 1992, Barbeau et al. 1993, Belanger et al. 1996)
RAT-neonatal and weanling	Th 4-11	(Stelzner et al. 1975, Weber and Stelzner 1977, Meisel and Rakerd 1982)
RAT-ADULT	mid-thoracic	(Freeman 1952, Freeman 1954, Meisel and Rakerd 1982, Bregman et al. 1993, Kunkel-Bagden et al. 1993, Zhang et al. 1994)
RABBITS- YOUNG	Th 12	(Fayein and Viala 1976, Viala et al. 1986)
RABBITS-ADULTS	Th 12	(Laughton 1924, Hinsey and Cutting 1932, Ten Cate 1964, Viala et al. 1986)
OPOSSUM	low thoracic-upper lumbar	(Hinsey and Cutting 1936)
PIGEONS	intumescentia lumbosacralis	(Ten Cate 1960, Ten Cate 1962)
FROGS		(Afelt 1963)

walking movements overground. In one cat, a second transection above the first spinal section did not change the locomotor behaviour. They insisted much on daily training as well as the fact that young animals performed much better than older animals.

Ten Cate also undertook a later study on spinal pigeons (Ten Cate 1960, 1962) and spinal cats (Ten Cate 1962). Using specially designed carriages, he showed that spinal pigeons could walk with normal extension of the toes during stance and were able to

propel the body forwards; it seems that, once initiated, they could maintain this walk through proprioceptive inputs from the moving legs themselves. Perineal stimulation and other stimuli modulated the frequency of stepping. Cats on the other hand could generate hindlimb movements only when the body was pulled forwards and the hindlimbs stretched, due to forelimb movements.

Laughton (1924) reported air stepping in chronic spinal rabbits which had the typical alternating configuration seen in dogs (Mark-time reflex) but not the in-phase coupling typical of rabbit locomotion. Ten Cate also described the locomotion of chronic spinal rabbits (1964) in a special carriage. Both synchronous bilateral and alternate movements could be elicited in these rabbits but could not be maintained for more than a few steps. In spinalised young rabbits (Fayein and Viala 1976) it appears easier to get both alternate and non-alternating gaits. Infant rabbits initially have normally an alternate pattern; by 20 days, they become exclusively in-phase (Viala et al. 1986). These authors made the important observations that rabbits spinalised 2 days after birth could be trained to have either a predominant alternate or non-alternating gait. These patterns were maintained after a second spinal transection. These respective patterns were also maintained in fictive conditions, suggesting that the training has had a major effect of the locomotor pattern which is expressed; this in turn implies a certain plasticity in the locomotor network, at least before descending pathways complete their connections with the cord (around day 18).

STUDIES IN CHRONIC SPINAL CATS

Work in the cat was rare before or around the seventies (Sherrington 1910b, McCouch 1947, Kozak and Westerman 1966, Afelt 1970, 1974). However, in 1973, two very influential papers appeared (Forssberg and Grillner 1973, Grillner 1973) describing that acute low spinal cats could walk with their hindlimbs on a treadmill when injected with an alpha-2 noradrenergic agonist, clonidine and that kittens, spinalised within a few days after birth (thus before they had expressed any locomotor pattern) could walk and gallop with their hindlimbs on a treadmill. These spinal kittens not only could walk with the hindlimbs on a treadmill with correct foot placement and support of the hindquarters but could also place their paw on a surface when the dorsum of the foot touched an edge (placing reaction; Grillner 1973, Forssberg et al. 1974) and could hop sideways.

A more complete account of the findings in chronic spinal kittens was published later (Forssberg et al. 1980a,b, Grillner 1981) and showed not only that the kinematics and the EMGs of spinal kittens were very similar indeed to normal cats but also that the spinal kittens had the ability to adapt their locomotion to the various speeds of the treadmill and even to asymmetrical treadmill speed. This emphasized the importance of peripheral afferent signals in adapting the locomotor pattern to external conditions. Further, these chronic spinal cats were shown to adapt to perturbations applied during the swing and stance phase and generate specific reflex compensatory responses in the various phases (see (Rossignol et al. 1988) for a review). This suggests that the spinal cord not only generates the locomotor pattern but that it can adapt it to external perturbations.

A report on adult chronic spinal cats (Eidelberg et al. 1980) stated that 2/3 of the cats had quasi normal stepping movements of the hindlimbs on the treadmill while 1/3 had persistent abnormal movements which could not even be described because they were so erratic. None of the cats were capable of weight support and a sling under the belly was used to test locomotion of all 4 limbs on the treadmill. It was shown that these cats had no weight support and no coordination between the forelimbs and hindlimbs and that even the spinal stepping had abnormal features such as a greater variability in hindlimb coupling, foot drag during swing and uncoupling between the knee and ankle. Further, once established, the locomotor pattern did not improve with repeated trials. This altogether rather negative report testing spinal cats on all 4 limbs obscured the fact that adult spinal cats could indeed

walk with their hindlimbs on a treadmill, much as the spinal kittens.

Along these lines of work, it was shown that the age of spinalisation and the amount of training on the treadmill (30 min 5 times a week) had important effects on the locomotor pattern (Smith et al. 1982, Bregman and Goldberger 1983, Robinson and Goldberger 1986b). Animals spinalised at 2 weeks of age had a much better locomotor performance than those spinalised at 12 weeks of age. Training in 12 week old cats had an observable effect on weight bearing during locomotion. The EMG pattern appeared normal in many respects, except that clonus was frequently observed. Even so, defects in the locomotor pattern such as uncoupling between the knee and ankle as well as an absence of yield in E2 phase of the step cycle were reported.

Work in adult chronic spinal cats (Rossignol et al. 1982, 1986, 1989a, Barbeau and Rossignol 1987, Belanger et al. 1996) has clearly established that the quality of locomotion is indeed improved by training and that the spinal locomotor pattern evolves with time. For instance, as time progresses, cats make larger steps at the same treadmill speed; this is achieved by a greater lengthening of the extensor burst relative to the flexor burst, a structure which resemble more the situation in the intact. In 3 cats it was found that cycle duration increased as a function of time but reached a plateau at around 3 months. All cats made plantigrade foot contact and could maintain the weight of the hindquarters by the third week. The important joint uncoupling described before and the absence of yield in E2 were not confirmed (see also: Lovely et al. 1990). However, foot drag was present in most cats during the first part of swing. This was interpreted as being due to a decrease in the delay between the onset of the knee flexor and the hip flexors so that both start more or less simultaneously in the spinal cat whereas normally the knee flexor first removes the foot from ground before it is brought forwards. It was also observed that Tibialis Anterior, an ankle flexor, also tended to be recruited earlier than in the intact which again could result in a foot drag if the foot is not already lifted from ground. In many other aspects however, the EMGs observed after spinalisation were similar to those observed before in cats chronically implanted with EMG electrodes before the spinalisation (Belanger et al. 1986, 1987, 1988a,b,c, 1989, 1996). Lovely et al. (1990), using force transducers placed on Soleus and Gastrocnemius Medialis, further emphasized that, although the force generated by spinal cats reaches the same level as normal cats, it declines rapidly during stance. This decrease in force may facilitate the premature onset of swing (Duysens and Pearson 1980) which could result in foot drag. On the other hand the force level recorded, at least in Soleus, would be large enough to participate in propulsion as suggested for the spinal kittens (Forssberg et al. 1980a).

The importance of regular daily training (even starting as late as 1 month after transection) was further emphasized by others (Lovely et al. 1986, 1990, Edgerton et al. 1991, Roy et al. 1992). This is of course of great interest in the clinical human situation, especially if training can be accelerated through the use of pharmacotherapy (see later). Another remarkable effect appears to be in the specificity of training. In contrast to spinal cats which had locomotor training, those that were instead trained only to stand for several months had a very poor locomotor performance on the treadmill (Edgerton et al. 1991). Since the difference between the behaviour of the two groups can hardly be explained by the state of the neuro-muscular apparatus, it is suggested that training of spinal locomotion is a form of spinal "learning" akin to the learned modifications of the H-reflex seen in monkeys after spinalisation (Wolpaw and Lee 1989).

Partial spinal lesions

Based on lesion studies, it was generally considered that pathways of the ventral and ventro-lateral quadrants of the spinal cord are important for the control of locomotion. Subtotal lesions of the spinal cord also point to the importance of the medial and mediolateral pathways in the control of locomotion (see: Eidelberg 1981, for a review of early literature on different subtotal lesions in primates

and non-primates). Sparing of at least part of a ventrolateral quadrant in the cat, and the associated labelling by HRP of neurones in the pontine and medullary formation, were claimed to be essential for recovery of locomotion in chronically lesioned cats (Afelt 1974, Eidelberg et al. 1981a, Contamin 1983) and monkeys (Eidelberg et al. 1981b). Evidence is however mounting that cats (Górska et al. 1990, 1993a,b, Brustein et al. 1993, 1994) and monkeys (Vilensky et al. 1992) can walk with the hindlimbs even after complete section of these pathways, although there are changes in the forelimb-hindlimb coupling. Extensive work by the group of Górska has been performed on this subject (Górska et al. 1990, 1993a,b, Zmysłowski et al. 1993, Bem et al. 1995). The recent work in our group (Brustein et al. 1993, 1994, 1995) on chronically implanted cats confirm that one of the main deficits of these cats with massive lesions of the ventral and ventrolateral tracts is the lack or instability of hind-fore-

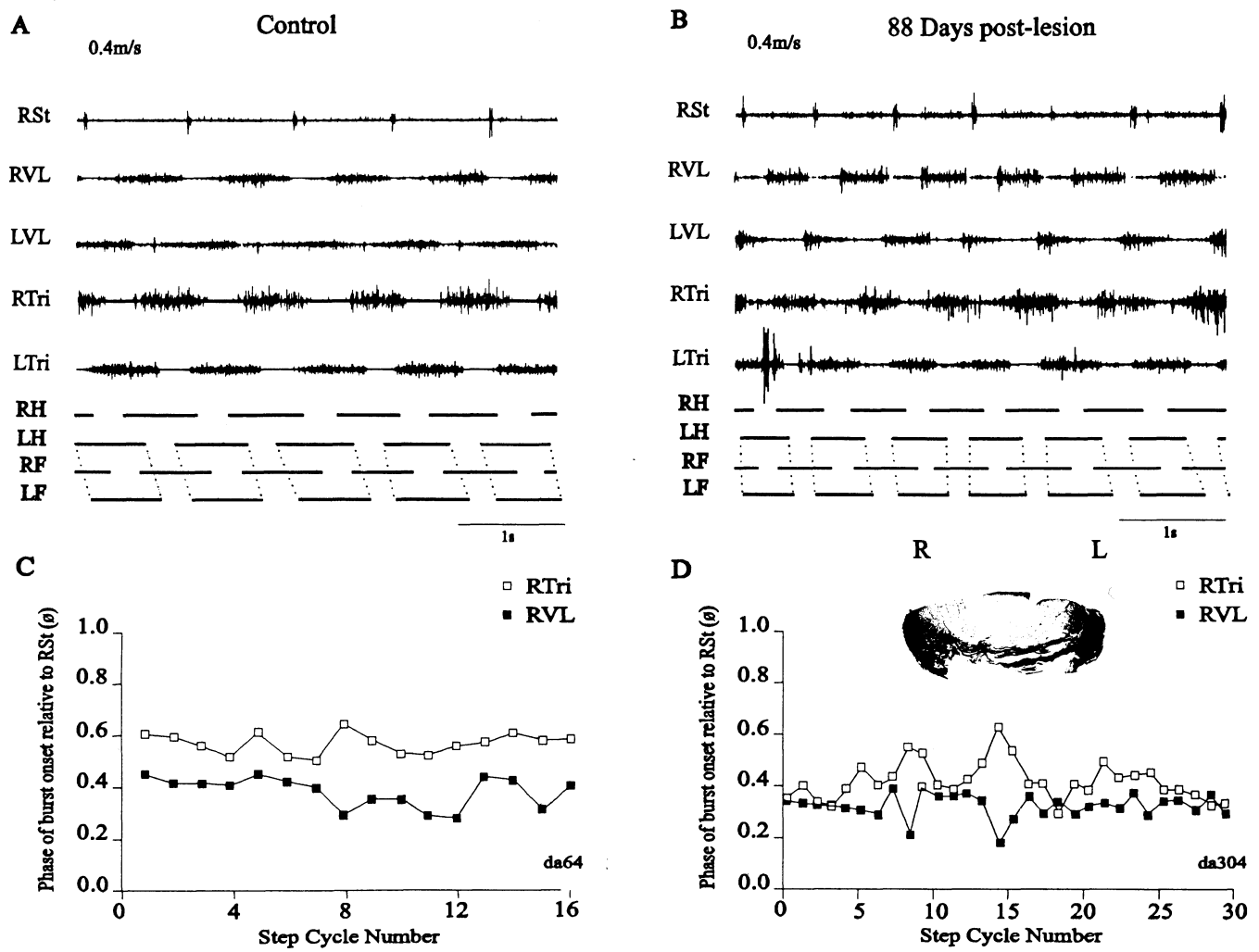

Fig. 1. EMG and foot fall pattern in a cat with a bilateral ventral and ventrolateral spinal cord lesion (the histological section is shown as an insert in D). A, control period. EMGs during walking at 0.4 m/s. St, Semitendinosus; VL, Vastus lateralis; Tri, Triceps brachii, lateral head. R, right; L, left. H, hindlimb; F, forelimb. B, same but 88 days after the lesion shown in D. C. phase plot of the onset RVL in the hindlimb and RTri in the forelimb to indicate the coupling between the fore- and hindlimb. The values are expressed as phases of the step cycle defined by the onset of RSt. Note the phase difference between the two is in the order of 0.25. D, same as C but 88 days post-lesion; note the tendency for a reduced phase coupling (tendency to pace). The insert in D is a cresyl violet staining of the lesion at its maximum.

limb coordination. Cats tend to increase the control over the forelimbs and also tend to pace even several weeks after the lesion (see Fig.1). After such massive lesions of the ventral and ventrolateral pathways, the remaining dorsolateral pathways are thus capable of triggering voluntary hindlimb movements and in part coordinate all 4 limbs favouring the most stable locomotor pattern (increase in the number of feet on the ground at all times). We have not found any foot drag in these cats, although lesions of the dorsolateral funiculus (Jiang and Drew 1996) produce such foot drag much as in the complete spinal cat.

About a week after a spinal hemisection at the low thoracic level, cats can readily walk overground with both hindlimbs; after a second transection at the midthoracic level contralaterally to the first section, cats still can regain voluntary locomotor functions overground, although the fore- and hindlimbs coupling may be lost (Kato et al. 1984). After a longitudinal split of the lumbar cord from L2-3 to L7-S1, cats can, after about 1 month, stand and walk with bilateral hindlimb coordination suggesting that the interlimb coordination can be assured by descending pathways (Kato 1988). After such a split and a further unilateral hemisection, the isolated spinal cord can eventually step even though it is isolated from supraspinal and contralateral inputs. However, it is difficult to assess the quality of such locomotion without further EMG data and especially kinematic data (Kato 1989, 1991). A list of some of the pertinent references on partial spinal lesions in relation to locomotion can be found in Table II.

Locomotor capabilities of primates and humans after spinal lesions

Philippson (1905) made some laconic comments on 3 spinal monkeys. Although it is clearly stated

TABLE II

List of references related to locomotor studies in various species after partial spinal lesions. In man, neurologically incomplete means that the patients still have some sensory-motor functions whereas neurologically complete means that the patients have no sensory-motor functions although the spinal cord is not completely severed

Chronic partial spinal section in different species

Species	Type and level of lesions	References
MAN	neurologically incomplete: various levels	(Fung et al. 1990, Wainberg et al. 1990, Stewart et al. 1991, Norman and Barbeau 1992, Barbeau and Fung 1994, Calancie et al. 1994, Barbeau and Rossignol 1994, Nathan 1994)
MAN	neurologically complete: various levels	(Bussel et al. 1988, Stewart et al. 1991, Wernig and Muller 1992, Dietz et al. 1994, Dietz et al. 1995, Wernig et al. 1995)
MONKEYS	various quadrants	(Eidelberg et al. 1981b, Vilensky et al. 1992)
MONKEYS	hemisection	(Aoki et al. 1991)
CATS	various quadrants	(Eidelberg and Stein 1974, Eidelberg 1981, Eidelberg et al. 1981a, Eidelberg et al. 1985)
CATS	ventral and/or ventrolateral	(Afelt 1974, Górska et al. 1990, Brustein et al. 1993, Górska et al. 1993a, Brustein et al. 1994, Brustein et al. 1995, Bem et al. 1995)
CATS	dorsal columns and/or dorsolateral and/or lateral funiculi	(Windle et al. 1958, English 1980, Contamin 1983, English 1985, Górska et al. 1993b, Zmyslowski et al. 1993, Jiang and Drew 1996)
CATS	simple and serial hemisections	(Kato et al. 1984, Masamichi et al. 1984, Kato et al. 1985, Kato 1988, Kato 1989, Kato 1991, Helgren and Goldberger 1993)

that locomotor movements were observed, we have unfortunately very few details. A major study was made by Eidelberg et al. (1981b) on macaque monkeys (spinalised at T8-T9). In contrast to the situation in cats (Grillner and Zangger 1979), DOPA did not induce locomotion in acute spinal monkeys. In the chronic state (up to 4 months), it was impossible to elicit locomotor movements even after clonidine. In monkeys with partial spinal lesions, it was concluded that the ventrolateral cord sector was crucial for locomotion and that the spinal stepping generator in monkeys was more heavily dependent on supraspinal inputs.

A reappraisal of the same data 10 years later (Vilensky et al. 1992) indicates that locomotion is possible in primates after very extensive but incomplete spinal lesions, that there is no specific correlation between the sparing of specific tracts and the recovery of locomotion (namely the ventrolateral tracts), and that there is some limited evidence of rhythmic hindlimb movements in the chronic spinal monkey. Recent evidence (Hultborn et al. 1993) on the marmoset, considered to be a relatively primitive primate in evolutionary terms, indicates that fictive locomotion can be induced after paralysis (clonidine or DOPA). Chronic hemisections in monkeys (Aoki et al. 1991) led to recovery of function after several months, apparently due to collateral sprouting of the contralateral cortico-spinal tract.

Evidence in Man is also not very clear (see Vilensky et al. 1992). Holmes (1915) and Kuhn (1950) describe such rhythmic locomotor movements of the lower legs in several patients having sustained a spinal cord injury during both world wars. Some more recent observations (Roby-Brami and Bussel 1987, Bussel et al. 1988, Dobkin et al. 1992, Calancie et al. 1994, Dietz et al. 1994, 1995, Wernig et al. 1995) also suggest that there might be some spinal circuits in man capable of generating a basic locomotor rhythmicity. Electrical stimulation of the spinal cord in complete anatomical paraplegic can evoke well organized rhythmic activity in the lower limbs (Rosenfeld et al. 1995). There is thus the possibility in man to generate involuntary rhythmic locomotor movements probably through circuits implicating the spinal cord and perhaps some brain stem structures. Other reports on brain death patients (Mandel et al. 1982, Hanna and Frank 1995) also suggest that such locomotor movements can be present for several days before the actual death, again suggesting that involuntary mechanisms may be implicated in the generation of locomotor rhythmicity in man. It is thus possible to think that such mechanisms could be facilitated through locomotor training and perhaps pharmacotherapy (see later). The work of several authors on humans suggest that this is a real clinical possibility (Barbeau and Rossignol 1994, Rossignol and Barbeau 1995).

PHARMACOLOGY OF LOCOMOTION AFTER SPINAL LESIONS

Given the fact that there are control mechanisms within the spinal cord and the brain stem which are crucial for locomotion, to what extent can we act on these mechanisms through the activation or inactivation of the receptors of the various neurotransmitter systems? Our attempts at initiating and modulating the spinal locomotor pattern in early spinal cats (within the first week or so after the lesion) and in chronic spinal cats that have already regained the ability to walk with the hindlimbs when placed on a treadmill have been summarized recently and most of the earlier references can be found in these reviews (Rossignol and Barbeau 1993, Barbeau and Rossignol 1994, Rossignol et al. 1995).

In brief, it appears that it is only the activation of the alpha-2 noradrenergic receptors (through agonists such as clonidine, tizanidine, oxymetazoline, the precursor DOPA or the transmitter itself, norepinephrine) which can trigger locomotion in early complete spinal cats. All other systems that we have tested (glutamatergic, serotonergic, dopaminergic) have failed in our hands to trigger sustained locomotion in the early spinal cat although they may do so in other mammal species or preparations, i.e. 5-HT and NMDA in neonatal rats (Cazalets et al. 1992),

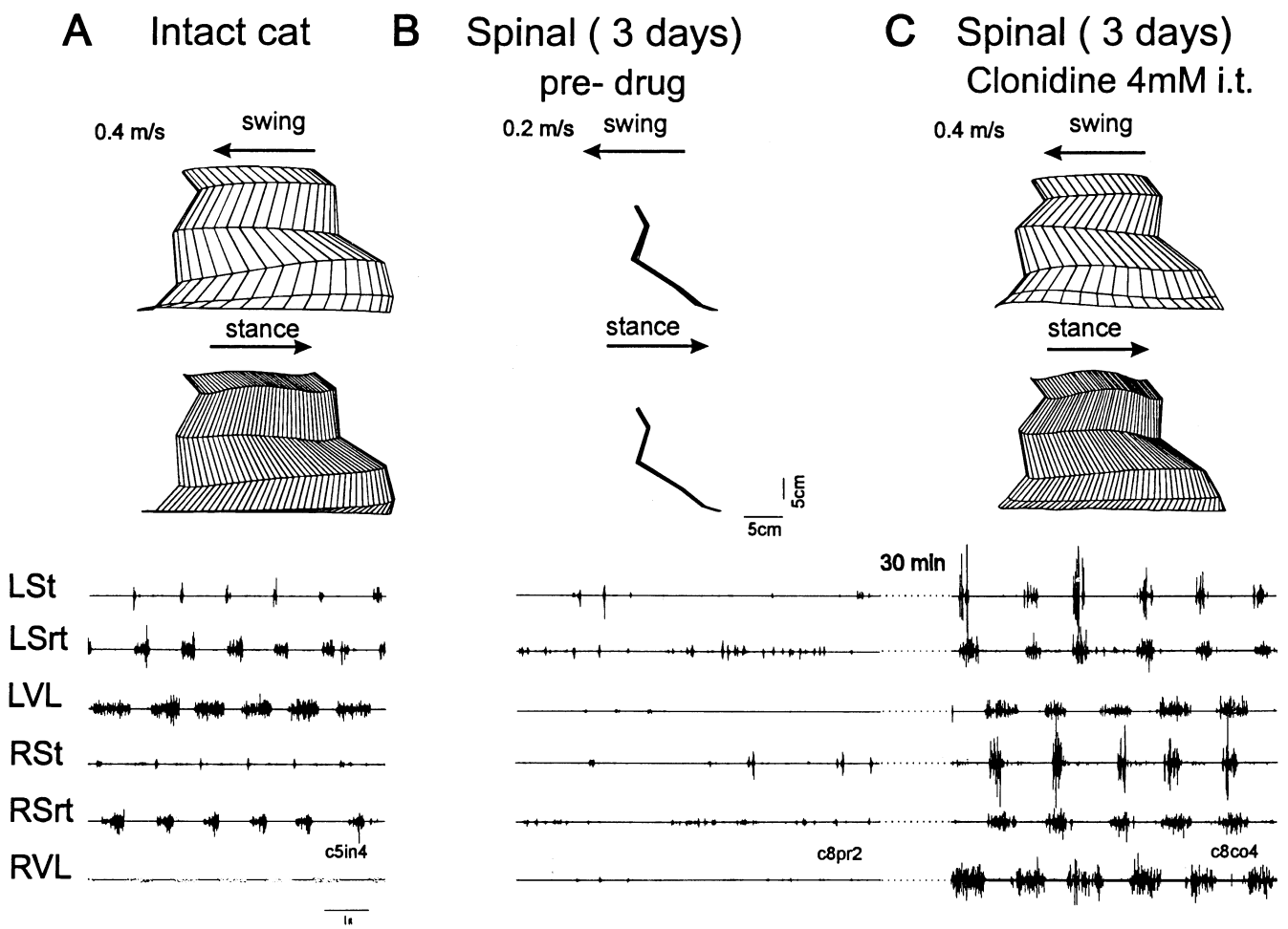

Fig. 2. Early-spinal (3 days) cat injected with intrathecal clonidine (4 mM). A, walking on a treadmill at 0.4 m/s during the control period before spinalisation. B, three days after spinalisation before injecting clonidine. C, thirty min. after i.t. clonidine. Muscles: Srt, Sartorius anterior; other abbreviations as in Fig. 1. Note that the gains of EMG are the same in the three panels. Arrows indicate the direction of the movement. The distance calibration in X is twice that in Y because the hip point is displaced by the amount of the displacement of the foot. Note in the stick figure of C a foot drag in the initial part of swing, a frequent defect in spinal cats which is enhanced by clonidine.

NMDA in decerebrate cats fictive locomotion (Douglas et al. 1993), 5-HT and dopamine in rabbits (Viala and Buser 1969).

Figure 2 illustrates the effect of an intrathecal (i.t.) injection of clonidine in a complete spinal cat. The left panel illustrates the locomotor pattern of the cat during the control period before spinalisation. Three days after spinalisation the cat is virtually motionless on the treadmill, the limbs being passively dragged on the treadmill belt. A few minutes after the i.t. injection of clonidine, the cat can step with its hindlimbs on the treadmill in a well coordinated pattern and continue to do so for several hours.

When the animals have recovered the ability to spontaneously walk with the hindlimbs on the treadmill belt without any external help (late-spinal cats: Barbeau and Rossignol 1987), then the different neurotransmitters may exert modulatory effects on the expression of the locomotor pattern. For instance, clonidine may markedly increase the duration of the step cycle (Barbeau et al. 1987, Barbeau and Rossignol 1991, Rossignol et al. 1995), whereas serotoninergic agonists may increase the amplitude of electromyographic activity (Barbeau et al. 1987, Barbeau and Rossignol 1990, 1991). Although NMDA does not appear to trigger locomo-

tion in the early-spinal cat, it does greatly increase the excitability of the spinal cat during walking as evidenced by frequently interspersed episodes of fast paw shake. AP5, an NMDA blocker may block locomotion of the chronic spinal cat which may then be reinstated with an intrathecal injection of NMDA (Chau et al. 1994).

The above results should be clearly interpreted within the context of a complete spinalisation where there is a complete disappearance or major reduction of the neurotransmitters below the lesion and in which receptor hypersensitivity may develop. This is important because the effect of the drugs may differ in animals with partial lesions walking voluntarily on all 4 limbs. In such animals, we have found that clonidine may be detrimental to walking by significantly decreasing the ability to sustain the weight of the hindquarters. In this context, it is worth mentioning that spinalisation may unmask excitatory alpha-1 effects, whereas without spinalisation or with incomplete spinal lesions, the inhibitory alpha-2 effects may predominate (Kehne et al. 1985). On the other hand, drugs that may exert an excitatory effects on motoneurones, such as alpha - 1 noradrenergic agonists (Methoxamine) or 5-HT agonists (quipazine) may be more helpful in improving the ability of these partially lesioned animals to walk with better weight support for longer period of time.

Figure 3 illustrates the locomotor EMG pattern of a cat 9 days after a severe (but as yet undocumented) lesion of the ventral and ventrolateral funiculi. The cat could hardly sustain its weight and had a disorganized locomotor pattern. After i.t. injections of noradrenaline, the EMG amplitude was much increased and the cat was able to walk steadily for a relatively longer time period and double its maximal walking speed (0.2 m/s to 0.4 m/s). This suggests that the enhanced excitability of the cord produced by noradrenaline does not interfere with voluntary control of the animal but rather that the animal can utilize this increased spinal excitability to achieve a better locomotor performance, which is really the main goal and hope of locomotor pharmacotherapy in spinal cord injured patients (Barbeau and Rossignol 1994).

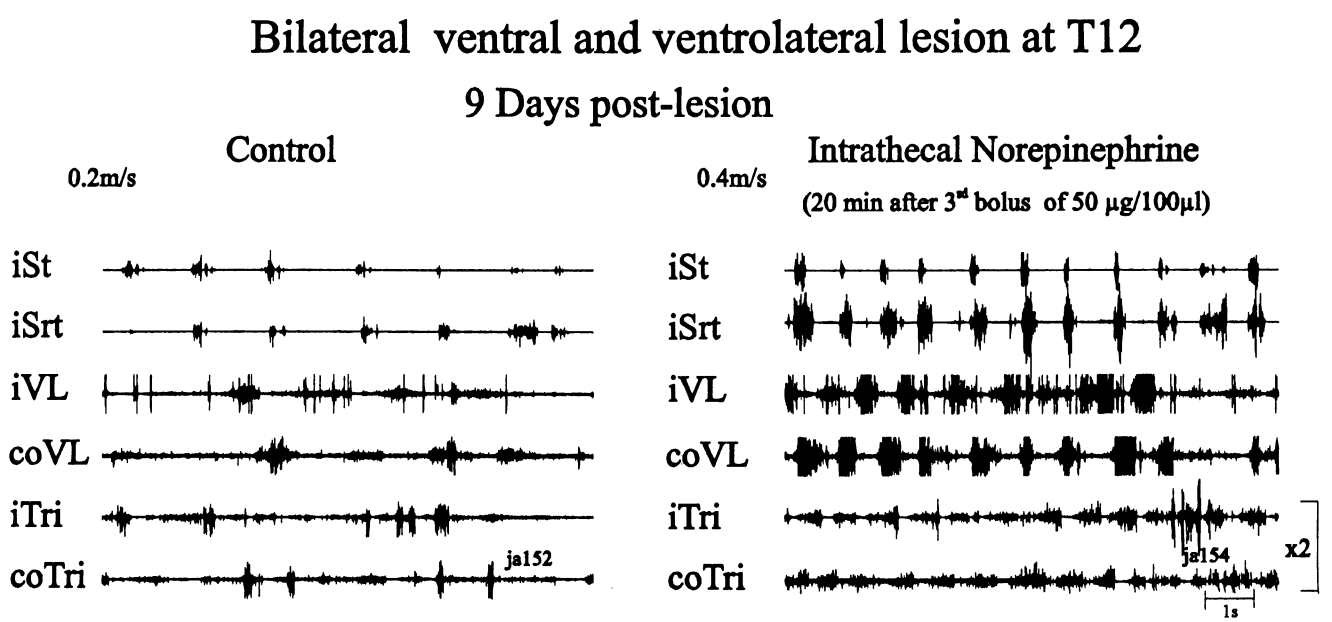

Fig. 3. Modulation of locomotion in a partially lesioned cat by i.t. administration of noradrenaline (NE) at 9 days post-lesion (large but yet undocumented spinal lesion because the cat is still alive). On the left is shown the EMG pattern of the cat walking at 0.2 m/s (its maximal speed performance) before the drug administration. On the right, the cat is walking at 0.4 m/s, 20 min after the 3rd dose of 50 µg/100 µl of NE i.t. (The other injections were given 1 and 1.5 h before). Abbreviations: are the same as in Figs. 1 and 2. Note saturation of the signal in the extensor muscles VL and that the rhythms of the hindlimb and forelimbs are different.

CONCLUSIONS

From these studies, we can conclude that, in most species, the locomotor program is innate and generated centrally in the spinal cord. After spinalisation, the locomotor capabilities change with time and training (plasticity) and locomotion can be adapted to speed and perturbations. Locomotion can be triggered by alpha-2 noradrenergic stimulation in early-spinal cats. In late-spinal cats, all neurotransmitter systems can on the other hand modulate the expression of the locomotor pattern. In normal conditions, it is possible that the locomotor program can be triggered through the action of several descending pathways. We have no indication that any particular descending pathway is unique or essential for triggering locomotion. Even cats with massive ventral and ventrolateral lesions can perform voluntary quadrupedal locomotion although there are major deficits in weight support and interlimb coordination. It is therefore possible to conclude that there is a spinal circuitry implicated in the generation of the locomotor rhythm, that this circuitry has some degree of plasticity which is essential for any potential benefit of locomotor training, that activity in this locomotor circuitry can be triggered or modulated by neurotransmitters as well as sensory inputs and finally that different descending pathways in the dorsolateral or the ventral-ventrolateral quadrants can trigger or modulate this circuitry. It is believed that these concepts are important and necessary for the design of locomotor rehabilitation strategies in patients with spinal cord injuries, especially when different approaches such as locomotor training, pharmacotherapy and functional electrical stimulation are combined (Barbeau and Rossignol 1994).

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