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Evidence for a spinal stepping generator in man. Electrophysiological study

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Review

Abstract. We present some evidences favouring the presence of a spinal stepping generator in humans. Electrophysiological studies have shown that the spinal cord even deprived of supraspinal influence can generate rhythmic activity, and that some elements of the spinal circuitry on which the generation of stepping rhythmic relies in lower vertebrates exist in man. Moreover, comparison of the variations of the polysynaptic spinal flexor reflex in normal subjects and paraplegic patients brought about some evidences that normal subjects use a spinal locomotor center. Nevertheless, these studies do not absolutely proove the existence of a central pattern generator in man.

Key words: man, spinal stepping generator, spinal flexion reflex, paraplegia

INTRODUCTION

The existence of the central pattern generator (CPG) for locomotion in lower mammals has been clearly demonstrated by Brown (1911) who showed that rhythmic stepping like activity observed in acute spinal cat was not due to a succesion of reflexes since it persisted after peripheral deafferentation of the distal stump of the spinal cord. Later on Perret (1976) showed that alternating neurogram activity persisted after curarisation of the animal. The physiology of the CPG has been reappraised by Lundberg's group (Jankowska et al. 1967, Lundberg 1981) and then extensively described in lower mammals (Grillner et al. 1973, Grillner and Wallen 1985). Spinal locomotor activity was mainly observed in acute spinal preparations after injection of cathecholaminergic drugs (Jankowska et al. 1967, Grillner et al. 1973). Spinal locomotor activity was also observed in chronic spinal cat spinalized as a kitten or if the spinal section was immediately followed by daily training on a treadmill (Barbeau and Rossignol 1987). In the chronic trained adult spinal cat, clonidine (which is a cathecholaminergic drug) is not necessary to induce rhythmic activity but it improves its amplitude and its regularity (Barbeau and Rossignol 1991). Similarly, spinal locomotor activity can be obtained in chronic spinal rats after transplanting embryonic cathecholaminergic cells below the level of the spinal transection (Yakovleff et al. 1989, 1995). In chronic spinal monkey, the existence of this CPG was first denied (Eidelberg et al. 1983). This assertion has been rediscussed by the same group and has led to less clear cut interpretations of the results (Vilenski et al. 1992).

The presence of a CPG in man is still debated. Usually, patients with a clinically complete spinal cord section clearly do not recover rhythmic alternating locomotor activity as expected, although encouraging results have been obtained recently (Wernig et al. 1992, Dietz et al. 1994) reviewed by Barbeau and Rossignol (1994). In addition, our group brought significant arguments favouring the presence of a CPG in patients with a clinically complete paraplegia. First, we demonstrated that flexor reflexes in paraplegic patients were always related to the CPG network (Roby-Brami and Bussel 1987, 1990, 1992). Secondly, we observed rhythmic spinal activity in a patient with a clinically complete spinal cord section (spinal myoclonus) (Bussel et al. 1987). I shall present new results obtained by studying the variations of flexion reflexes during walking in normal and paraplegic patients.

FLEXION REFLEXES AND CPG

It has been shown that electrical stimulation of a distal nerve of the lower limbs (purely cutaneous-sural, or mixed nerve tibial posterior at the ankle) can elicit, in normal subjects as well as in patients with a lesion of the central nervous system, a spinal flexion reflex in flexor muscles. The same stimulation of the Flexor Reflex Afferents (FRA) in patients with a complete spinal cord section induced two EMG responses in the ipsilateral flexor muscles (Roby-Brami and Bussel 1987). The early response (latency of about 100 ms) is not different from the classical flexion reflex observed in normal humans as well as in animal experiments. The second response is characterized by a lower threshold, a generalized distribution in ipsilateral flexors and a longer latency (150-500 ms) which increases with either increasing intensities or increasing durations of the stimulation. We demonstrated (Roby-Brami and Bussel 1987) that the second response, and its latency increase, was directly induced by the electrical stimulation and not due to an effect of a preceding motor discharge. This shows that the long latency flexor reflex in humans has a long central delay and thus is similar to the late flexion reflex described in the acute spinal cat with DOPA. The works from Lundberg's group and recently by Gossard et al. 1994) have shown that the internuncial network released by DOPA is related to the CPG. We demonstrated in man two important characteristics of the DOPA network observed in animal experiments:

FRA stimulation induced presynaptic inhibition of Ia terminals (Roby-Brami and Bussel 1990). This

has been shown by studying the amount of monosynaptic Ia facilitation brought about on soleus alpha motoneurones by a heteronymous Ia volley from crural nerve. In 5 patients we found that Ia facilitation is depressed 200 to 500 ms after FRA stimulation (that is to say during the long latency flexor reflex).

FRA stimulation induced a premotoneuronal inhibition of contralateral late reflex in flexor muscles (Roby-Brami and Bussel 1992). The late flexion reflex obtained in one limb is inhibited by FRA stimulation of the other limb. We can assume that this inhibition is premotoneuronal since the flexor alpha motoneurone is not inhibited at this time (it can discharge through the early flexor reflex pathways). These three features indicate that the organization of the neural spinal networks in paraplegic patients is similar to the DOPA network observed in animal experiments and therefore to the CPG.

SPINAL MYOCLONUS

Since Lhermitte (1919) and Kuhn (1950) it is known that the human spinal cord deprived from supraspinal influences can generate rhythmic involuntary movements. We have had the opportunity to examine a patient with a complete spinal cord section who exhibited rhythmical contractions (0.5 Hz frequency) of the trunk and lower limb extensor muscles (Bussel et al. 1988). It is not possible in man to perform large peripheral deafferentation (Brown 1911) or to study fictive locomotion (Perret 1976) as in animal experiments. Nevertheless several arguments indicate that the rhythm is unlikely to be due to a peripheral loop but probably to an intrinsic spinal activity. Three arguments favour that this myoclonus could be due ιo the activation of the spinal stepping generator. First, this rhythmic activity could be induced, interrupted or modulated by FRA stimulation, secondly, in some, circumstances an alternating flexion-extension activity was observed and lastly animal experiments have shown that the spinal stepping generator can induce rhythmic bursts of extensor motoneurones as observed in our patient.

VARIATION OF FLEXION REFLEX DURING WALKING IN NORMALS AND PARAPLEGIC PATIENTS

In normal subjects and paraplegic patients able to walk we studied the variations of the early components of the polysynaptic flexion reflex (EMG activity recorded between 90 and 130 ms after tibial posterior nerve stimulation). In normal subjects we observed very few variations of the EMG response during the different phases of gait, by contrast in paraplegic patients the polysynaptic response varied in parallel with the EMG activity recorded in flexor muscles (it increased during the swing phase of gait). These results could indicate that in paraplegic patients the command of locomotor activity is done through the pathways of the early flexion reflex, and in normal subjects through another pathway (CPG?). Another explanation of our results can be proposed with the results presented by Rossignol (personal communication). He demonstrated that during the swing phase of gait, the CPG induces a presynaptic inhibition of FRA. In normal subjects this activity of the CPG could explain why the flexion reflex trigerred by the FRA did not vary in the same way as the flexor alpha motoneurone excitability (the FRA being presynaptically inhibited): this suggests that in paraplegic patients the CPG is non active because the flexion reflex increases during the swing phase of gait.

CONCLUSION

As claimed by Illis (1995) these studies do not absolutely proove the existence of a central pattern generator in man. Nevertheless there is some evidence that the spinal cord even deprived of supraspinal influence can generate rhythmic activity, and that some elements of the spinal circuitry on which the generation of stepping rhythms relies in lower vertebrates exist in man. The presence of a spinal CPG in paraplegic patients raises the hope that it could be activated by adequate training, pharmaco-

logical activation using cathecholaminergic drugs or maybe in the future by neural transplants.

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