EVALUATION OF POSSIBLE MECHANISMS OF ACTION OF SPINAL CORD STIMULATION

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ABSTRACT

Possible mechanisms which may play a part in producing the improvements seen on spinal cord stimulation are considered in relation to the pathophysiology of multiple sclerosis, and to the effects that a lesion may have on the central nervous system.

There is no direct evidence that impulses generated by spinal cord stimulation and transmitted through partially demyelinated fibres will help to restore them to normal function by, e.g. hastening remyelination, though reductions are seen in the latencies of brain stem evoked potentials which may be related to a change in conduction velocities of abnormal fibres. It is not know whether alteration in the ionic micro-environment due to stimulation occurs or not. Synaptic transmission is impaired in multiple sclerosis partly because reduced inputs cause a reduced central excitatory state and partly because of a specific blocking factor. Stimulation would improve inputs to synapses both directly due to stimulation of ascending sensory pathways and also indirectly as a result of increased motor activity. Evidence for improved synaptic transmission comes from the observation of the increased amplitude of the N11 component of the cervical somato-sensory evoked potential on stimulation. Stimulation may encourage the adaptive changes that normally take place in the central nervous system in response to a lesion.

In addition to examining the possible general effects of stimulation on the central nervous system, this paper also considers the effects which may be produced through stimulation of specific tracts. The tingling sensation produced by stimulation in patients who respond favourably indicates that primary afferent fibres from regions caudal to the electrodes are being excited. It is possible that spinal cord stimulation may alter the effectiveness of the synapses of primary afferent cutaneous fibres which are relatively ineffective at exciting cells above and below their own segment but under certain circumstances these synapses become effective. A different approach to considering which tracts are stimulated by epidural electrodes is to infer them fron the observed clinical effects. This approach is illustrated by considering the clinical changes seen in bladder function.

INTRODUCTION

Spinal cord stimulation has a beneficial effect on some patients with M.S. and possibly with neurological deficit due to other disease. There is clinical and physiological evidence that the benefits seen are not due to a placebo effect. This paper considers the mechanisms which may play a part in producing the improvements seen with spinal cord stimulation.

PATHOPHYSIOLOGY OF M.S.

The characteristic lesion of M.S. is demyelination of nerve fibres, and many of the observed features of the disease may be attributed to conduction block in these fibres (1). There is, however, some evidence of synaptic blockade as well.

Conduction Block

Impulses reaching a demyelinated length of axon are blocked or transmitted slowly. Partially demyelinated fibres have a long refractory period, increasing, as the extent of demyelination increases, from 1.0-2.2 msec in one study (2), though much higher values can occur (3). A slight rise in temperature may lead to total block of conduction. Lowering the concentration of calcium ions in the fluid bathing the axon improves conduction and the *in vitro* studies of Schauf and Davis (3) have predicted that agents prolonging the sodium conductance of the axon membrane should improve transmission in the affected fibres.

Synaptic Blockade

There is good evidence for a blocking factor in the plasma of M.S. patients (1) but its role in the disease process in unknown. Reflex studies which might show a synaptic blocking effect have shown only delayed response times. The cervical sensory evoked potential, however, has a reduced amplitude in M.S. and El-Negamy and Sedgwick (4) have given evidence that the N11 wave is produced post-synaptically in the dorsal horn of the cord and a reduced amplitude of N11 could be explained on the basis of synaptic blockade.

EFFECTS OF A LESION ON THE CNS

The effect of a CNS lesion includes not only specific deficits due to loss of functions subserved by the structures damaged but also more widespread effects on CNS function as a whole, and this latter effect may be of greater importance. A patients' neurological state is a product of the spatio-temporal pattern of firing in the neurones. This is influenced by the central excitatory state, a somewhat loose concept which refers to the level of excitability and embraces sensory information from the environment, sensory information generated by motor activity, and information from within the CNS. The effect of a CNS lesion will be to reduce this information. Furthermore, destruction of a major input to a neurone or neurone pool will not only have a negative effect; it will also have the positive effect of making minor inputs relatively more important.

The CNS may respond to the lesion by active reorganisation (5, 6) involving mechanisms which are known to be operative in neurogenesis and in the maintenance of function in the face of the naturally occurring loss of neurones.

There is evidence that neurones can support a larger terminal arborization than they usually do. An increase in terminal innervation is called sprouting and has been demonstrated in different species using different techniques (7-9). In addition, changes in the structure of undamaged synapses and an increase in the territory of functional axon terminals (10) indicates that connectivity can itself be altered by environmental change. There is improved connectivity in the fibres which have the heaviest input - a fact from which the concept of synaptic competition has been derived.

POSSIBLE EFFECTS OF STIMULATION

In the light of what has been said above, it may be concluded that there are several possible ways in which stimulation may help to reverse the abnormalities seen in the spatio-temporal pattern of impulses that occurs as a result of a lesion: a) direct effect on demyelinated fibres; b) effects produced by stimulation of damaged and undamaged pathways on synaptic transmission and hence on the central excitatory state; and c) encouragement of the adaptive changes that normally take place in the CNS in response to a lesion.

a) Direct Effect on Demyelinated Fibres

Demyelinated fibres fail to transmit at high frequencies (vide supra). The lowest frequency at which failure occurred in the study of MacDonald and Sears (2) was 290 per second, which is an order of magnitude higher than the frequency given in spinal cord stimulation (33 per second). It is probable, therefore, that impulses are transmitted through partially demyelinated fibres due to spinal cord stimulation but there is no evidence to suggest that this helps to restore them to normal function by, e.g. hastening the remyelination which is known to occur in the CNS (11). Nevertheless, the very striking reductions in the latencies of the brain stem evoked potential that we have observed on spinal cord stimulation (12) do suggest that the conduction velocities of the relevant fibres have been increased. Hill (13) demonstrated an increase in nerve diameter after repetitive stimulation of giant nerve fibres and Edds (14) demonstrated hypertrophy of nerve fibres in functionally over loaded muscles. An alteration in nerve fibre diameter would produce a change in the conduction velocity which would in turn lead to an alteration in the central path of stimulation. At the present time, therefore, structural alterations in nerve fibres as a result of spinal cord stimulation cannot be ruled out.

The only definite effect spinal cord stimulation is known to have on the ionic micro-environment surrounding the fibre is to increase extra cellular potassium (15) due to the continuous passage of impulses but it is not known whether this will be beneficial. Whether repetitive depolarisations due to the electrical stimulation causes the sustained increase in sodium conductance that Schauf and Davis (3) consider would improve transmission in affected fibres is not known. Spinal cord stimulation may alter the micro-environment in the region of the electrodes in other ways. It has been shown that strong stimulation may damage the blood brain barrier and less strong stimulation could cause some change in blood flow (16).

b) Effects Produced by Stimulation of Damaged and Undamaged Fibres on Synaptic Transmission

Synaptic transmission is impaired in M.S. partly because reduced inputs cause a reduced central excitatory state and partly because of a specific blocking factor. Stimulation of normal pathways at any frequency or of

undamaged pathways below the frequency at which blocking occurs would increase inputs both directly and also via any motor activity that was induced. (Wall (17) has suggested that dorsal column impulses may initiate cortical activity which will in turn set afferent systems to detect particular events and activate motor systems to produce movements which will generate further sensory information.) Furthermore, transmission at synapses receiving inputs from stimulated fibres would be improved by an alteration in the characteristics of those synapses, occurring in response to repetitive stimulation; in other words, plastic changes may occur at the synaptic zone. Such changes following repetitive stimulation have been demonstrated by de Robertis (18) in rabbits. Structural changes in synapses following repetitive stimulation have also been shown by Illis (19). Affected synapses in the cats' spinal cord enlarge to sizes similar to those of Clarke's column synapses and have similar light microscopic appearances. Clarke's column synapses have an extremely high efficiency of transmission (20). Conversely, tetanus toxin which has a specific action at inhibitory sites in the CNS produces morphological synaptic changes (21). Furthermore, it is possible to produce altered function in the visual system by altering the environment (22). Antidromic stimulation of the cat pyramidal tract produces an increase in the size of receptive fields of neurones, enhances excitability and may produce sensitivity to new modalities (23).

El-Negamy and Sedgwick (4) showed that in seven out of eight patients receiving spinal cord stimulation there was a striking increase in the amplitude of the N11 wave of the cervical somato-sensory evoked potential on stimulation. Furthermore, in two patients who relapsed and recovered, the N11 wave decreased and recovered also. They have given evidence that the N11 wave of the CSEP is produced post-synaptically in the dorsal horns of the spinal cord. It would seem, therefore, that we have direct evidence of changes in the synaptic zone in at least one area of the central nervous system as a result of spinal cord stimulation.

c) Encouragement of the Adaptive Changes that Normally Take Place in the Central Nervous System in Response to a Lesion

In the presence of the reduction of input to synapses that occurs as a result of a lesion, improved efficiency of transmission will of course count as an adaptive change. Whether other adaptive changes such as terminal sprouting are encouraged by spinal cord stimulation is at present uncertain. (It may indeed be the case that terminal sprouting may have a detrimental effect.)

PROBABLE TRACTS STIMULATED

We have so far talked only in general terms about the effect of stimulation. However, the effects observed in patients have been very specific - for example improvement in bladder function may occur without improvement in other aspects of the disease. The influence of stimulation must, therefore, be due to stimulation of specific tracts as well as to a general effect on the nervous system.

The one consistent feature of all patients who have responded favourably to spinal cord stimulation has been the presence of a warm, pleasant tingling sensation extending into both legs. To produce this sensation the stimulating electrodes need to be over the dorsal columns and at or close to the midline. Radicular sensations may co-exist but are not associated with clinical improvement. It appears that excitation of the dorsal columns is a *sine qua non* for a favourable clinical effect.

A number of fibre systems are present in the dorsal columns. Most numerous are the central axons of primary afferent fibres carrying information from low threshold cutaneous pressure receptors. A smaller number carry proprioceptive information. It has been estimated that only 25 per cent of these fibres ascend as far as the nucleus gracilis and cuneatus in the medulla while the remainder terminate at the dorsal horns above or below the root entry zone. A group of fibres subserving bladder sensation ascend in the dorsal columns and are located superficially, close to the midline. There are descending fibres which run from rostral to caudal parts of the dorsal horn (24) and propriospinal fibres interconnecting the grey matter two to five segments both rostrally and caudally.

The tingling sensation produced by stimulation indicates that the primary afferent fibres from regions caudal to the electrodes are being excited. One must presume that other fibres, whether primary afferent or propriospinal, of similar size and with similar thresholds, must also be excited. Some patients have reported tingling sensations referred to dermatomes several segments higher than the rostral electrode. This is probably due to stimulation of the descending branches of primary afferent fibres, some of which make up the comma tract. Higher stimulus strengths will produce muscle twitches of the appropriate segment and we have observed pallor of the skin and piloerection indicating spread to motor neurones or ventral roots and to pre-ganglionic sympathetic fibres.

Most of the synapses activated by spinal cord stimulation will be in the dorsal horn, though a few will be in the nucleus gracilis. It is clear from studies of Brown and others (25, 26) and those of Wall and Weiman (27) that impulses in dorsal column fibres will be distributed along the length of the dorsal horn up to the level of the stimulating electrodes and beyond due to excitation of the comma tract. The distribution of propriospinal synapses is not known in any detail but appears to be to the dorsal horns also.

Are the Clinical Benefits of Spinal Cord Stimulation Explicable in Terms of the Ascending Impulses to Nucleus Gracilis?

Spinal cord stimulation produces a continuous sensation which is pleasant but becomes regarded as neutral. It does not interfere with sleep or any other activities, though it may produce significant elevation of both tactile and vibratory thresholds (28). Although it has an alerting effect initially, it appears to produce no behavioural change and, so far as one can say, higher mental function and conscious experience are not changed by it. The contingent negative variation is unchanged by spinal cord stimulation suggesting it has no effect on motivation levels or attention (29). The EEG is unchanged by stimulation but Blair et al (30) have reported a reduction in the late components of the somato-sensory evoked response. Although it cannot be denied that spinal cord stimulation may act by inducing events above the cord, it seems more logical at present to consider the effects on the cord itself.

As most of the synapses excited by spinal cord stimulation lie in the dorsal horns, any interpretation of the action of spinal cord stimulation must rest heavily on the known physiology of this part of the spinal cord. This area is concerned with the reception, modulation and transmission of cutaneous sensory events, including noxious events. It is believed to be the site of the "gate" in the gate control theory of pain (31) and indeed spinal cord stimulation was first used to relieve pain by closing this "gate".

Devor, Merrill and Wall (32) have demonstrated that many of the synapses of primary afferent cutaneous fibres are relatively ineffective at exciting cells above and below their own segment but under certain circumstances, such

as blockage of the normal afferent input, the synapses become effective (33). It is possible, therefore, that spinal cord stimulation may alter the effectiveness of these synapses, an idea open to experimental verification.

Probable Tracts Stimulated Inferred from Clinical Effects

A different approach to considering which tracts are stimulated by epidural electrodes is to infer them from the observed clinical effects. This may be illustrated by considering the example of the clinical changes seen in bladder function.

The most obvious therapeutic effects seen are:

1. Control of the uninhibited contractions of the bladder wall that produce frequency, urgency and urge-incontinence; and

2. Restoration of previously absent or impaired bladder sensation,

Micturition is a complex act and normal control of micturition depends upon spinal and supraspinal control of the reflex detrusor contractions that occur as the result of stretching the bladder wall with urine, and upon ascending impulses informing the subject of the state of fullness of his bladder. There are three descending pathways controlling reflex micturition (34): the lateral, ventral and medial reticulo-spinal tracts. The first two tracts are located, at the level of the spinal cord, in the lateral white columns, where Fog (35) has shown that plaques of demyelination occur very frequently. Stimulation of the ventral reticulo-spinal tract in animal experiments has an inhibitory effect on detrusor muscle, resulting in marked relaxation of the bladder (36). The effect of stimulation may, therefore, be as Abbate et al had suggested (37) due to improved conduction in reticulo-spinal fibres. An alternative explanation is that stimulation of the sympathetic outflow to the bladder which in the cat has an inhibitory effect on bladder tone and raises the threshold for micturition (38) may suppress detrusor contractions. Studies we have done on cutaneous blood flow in the lower limbs with seven patients before and during stimulation do not show the reduction in blood flow that one might expect from increased sympathetic activity. Recent work, however, (39) has indicated that bladder wall relaxation is a beta-adrenergic effect whereas cutaneous vasoconstriction is, of course, and alpha-adrenergic.

Turning to the improvements noted in bladder sensation, it is relevant that the so called pelvic sensory vagus fibres, conveying information about the passive distension of the bladder and warning of impending micturition, ascend in the superficial layer of the dorsal colums close to the midline (34). Fibres in such a position would be well placed to be stimulated by midline dorsal electrodes; and yet patients do not complain of a feeling of fullness when the spinal cord is first stimulated.

CONCLUSION

The purpose of this survery of possible mechanisms of action of spinal cord stimulation has been to try to identify processes in the CNS which may be amenable to modification for therapeutic purposes. Other mechanisms of which we are not aware may also be important and we have not intentionally excluded them. Spinal cord stimulation and similar work shows that some degree of restoration of neurological function can be achieved and full advantage of the techniques can only be taken if a rational basis for them can be established.

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