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PATHWAYS INVOLVED IN THALAMIC VENTROBASAL STIMULATION FOR PAIN RELIEF: EVIDENCE AGAINST THE HYPOTHESIS VB STIMULATION → ROSTROVENTRAL MEDULLA EXCITATION → DORSAL HORN INHIBITION

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SUMMARY - Despite its use for a long time, the way thalamic ventrobasal (VB) stimulation acts to produce pain relief is still unknown. One of the most accepted hypotheses, sponsored by Tsubokawa among others, proposes that VB stimulation excites raphespinal and reticulospinal neurons of the rostroventral medulla which in turn send respectively inhibitory serotonergic and noradrenergic axons through both dorsolateral funiculi (DLF) to the dorsal horn (DH) nociceptive neurons; this pathway would be the same as is involved in periventricular-periaqueductal gray (PVG-PAG) stimulation induced inhibition of DH nociceptive neurons. This hypothesis implicates the necessity of DLF intactness; in fact, it was showed that section of bilateral DLF inhibits the response of DH nociceptive neurons to VB stimulation. If the above mentioned hypothesis is correct, one could expect that unilateral VB stimulation would produce bilateral pain relief, VB and PVG stimulation would be useful for treating the same modalities of pain and that in patients with central cord-based pain harboring complete cord transection, VB stimulation would not work at all. In order to check these possibilities, the patiens with central cord-based pain admitted to the Division of Neurosurgery, Toronto Hospital between June 1978 and July 1991 to undergo deep brain stimulation (DBS) were reviewed. Sixteen patients were operated on. Based on clinical criteria, four out of these sixteen patients were thought to present complet cord transection (all four were men, with an average age of 48 years and pain secondary to cord injury). The effectiveness of the procedure was evaluated in this subset of patients: 75% of them enjoyed excellent pain relief with VB stimulation; PVG stimulation, however, performed in three out of these four patients, did not produce pain relief. Besides, our clinical experience has demonstrated that VB stimulation is effective in treating only contralateral pain.These results, as well as certain experimental data provided by a review of the literature, seem to provide evidence enough to contest Tsubokawa's hypothesis.

KEY WORDS: pain, analgesia, electrical stimulation therapy, thalamic nuclei, thalamus, stereotaxis.

Vias envolvidas no alívio da dor pela estimulação talâmica ventrobasal: evidência contra a hipótese estimulação ventrobasal → excitação do bulbo rostroventral → inibição do corno dorsal

RESUMO - A despeito de seu uso há longo tempo, a maneira pela qual a estimulação talâmica ventrobasal (VB) produz alívio da dor é ainda desconhecida. Segundo uma das hipóteses mais aceitas, defendida por Tsubokawa dentre outros, a estimulação de VB excita neurônios rafe-espinhais e reticulo-espinhais do bulbo rostroventral, os quais por sua vez emitem respectivamente axônios serotoninérgicos e noradrenérgicos inibitórios para os neurônios nociceptivos de ambos os cornos dorsais através dos funículos dorsolaterais da medula espinhal; essa via é a mesma proposta para a inibição dos neurônios nociceptivos dos cornos dorsais pela estimulação da substância cinzenta periventricular-periaquedutal (PVG-PAG). Tal hipótese, obviamente, subentende a

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necessidade da integridade dos funículos dorsolaterais da medula; de fato, já foi demonstrado que a secção desses funículos inibe a resposta dos neurônios nociceptivos dos cornos dorsais à estimulação de VB. Se a hipótese mencionada for correta, poder-se-á esperar que: (1) a estimulação unilateral de VB produza alívio bilateral da dor; (2) a estimulação de VB e PVG-PAG sejam úteis para tratar as mesmas modalidades de dor; (3) a estimulação de VB seja ineficaz em pacientes com secção medular completa apresentando dor central de origem medular. Para se avaliar essas possibilidades, foram revistos os pacientes com dor central de origem medular admitidos à Divisão de Neurocirurgia do Toronto Hospital entre junho 1978 e julho 1991 para serem submetidos à estimulação cerebral profunda. Dezesseis pacientes foram operados nesse período, quatro dos quais apresentavam lesão medular completa, segundo critérios clínicos. Todos eram homens, com média de idade de 48 anos e com dor secundária a traumatismo raquimedular. A eficácia da estimulação cerebral profunda foi avaliada nesse subgrupo de pacientes: 75% deles (3 dentre 4) apresentaram excelente alívio da dor à estimulação de VB; a estimulação de PVG, porém, realizada em três desses quatro pacientes, foi ineficaz em todos eles. Além disso, a experiência clínica tem demonstrado que a estimulação unilateral de VB só é eficaz para o tratamento de dor contralateral. Esses resultados, bem como certos achados experimentais fornecidos pela revisão da literatura, parecem prover evidência suficiente para contestar a hipótese de Tsubokawa.

PALAVRAS-CHAVE: dor, analgesia, estimulação elétrica, núcleos talâmicos, tálamo, estereotaxia.

Neural injury pain is a chronic pain syndrome secondary to a lesion of the central (central pain) or peripheral (deafferentation pain) nervous system[13]. Its treatment is a very difficult matter and has challenged neurosurgeons over the years. Many surgical strategies have been proposed, varying from destructive to modulatory procedures. According to Tasker, destructive procedures have only, if any, a transient effect[13]. The best form of treatment of central pain (mainly its steady burning-tingling component) seems to be thalamic ventrobasal (VB) chronic stimulation[8-11, 13]. VB stimulation was first performed by Mazars[12] and, despite its use for about thirty years, the way it acts to produce pain relief is still a matter of great controversy. Many hypotheses have been suggested trying to explain it[1, 2, 4, 7, 12, 15-19]. One of the most accepted is that sponsored by Tsubokawa, among others. Tsubokawa et al.[15, 17, 18] proposed that VB stimulation produces pain relief by excitation of the rostroventral medulla (RVM), which, in turn, projects inhibitory descending axons through both dorsolateral funiculi (DLF) of the spinal cord to the dorsal horn nociceptive neurons (Fig 1). Gerhart et al.[7] demonstrated that such inhibition is abolished by a spinal cord lesion including both bilateral DLF and the ventral part of the ipsilateral lateral funiculus. Based on these observations, one could expect that unilateral VB stimulation would produce bilateral pain relief, VB and periventricular-periaqueductal gray (PVG-PAG) stimulation would be useful for treating the same modalities of pain (the pathway involved in DH nociceptive neurons inhibition by PVG-PAG stimulation is the same as that proposed for VB stimulation) and that in patients with complete cord transection presenting with central cord-based pain, VB stimulation would not work at all.

This paper provides evidence against the above mentioned hypothesis.

PATIENTS AND METHODS

Between June 1978 and July 1991, sixteen patients with intractable central cord-based pain were admitted to the Division of Neurosurgery, Toronto Hospital, to undergo deep brain stimulation (DBS).

In order to check the reliability of Tsubokawa's hypothesis, the efectiveness of DBS was evaluated in selected patients, thought to harbour complete spinal cord transection, based on the following criteria: complete motor and sensory deficit and absence of evoked pain - hyperpathia and/or allodynia - below the lesional level (Tasker[13] suggests that evoked pain is conducted through "normal" pain pathways; so, its presence below the lesional level would suggest an incomplete cord lesion).

Four patients met these criteria and were characterized as follows.* Sex: 4 men. * Average age: 48 years (42-53 years). * Etiology: cord injury. * Site of injury: cervical cord: 1 patient; thoracic cord: 3 patients. * Pain character: constant pain, 4 patients; intermittent pain, 2 patients; evoked pain, no patients; associated nociceptive pain,1 patient. * Pain distribution: bilateral, 4 patients.

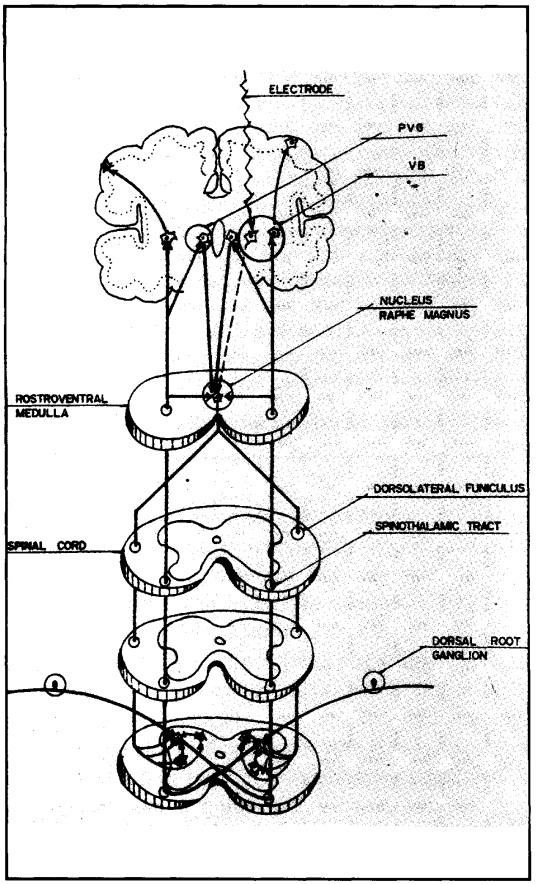

Fig 1. Diagram of the pathway mediating inhibition of spinothalamic tract (STT) cells by thalamic ventrobasal (VB) stimulation, according to Tsubokawa, as well as the possible pathway involved in periventricular gray (PVG) inhibition of STT cells. It also shows the STT and its collaterals to areas related to pain modulation. Legend:→ = excitation; ⊣ = inhibition.

Once the Leksell frame was in place, ventriculography was performed and the coordinates of anterior and posterior comissures (AC and PC) obtained (the four patients of this series were operated on before 1986, when CT started to be used to calculate the coordinates of AC and PC). These coordinates were fed into a software program which contained a digitized set of sagittal diagrams from the Schaltenbrand and Bailey atlas. A set of sagittal diagrams were then drawn, shrunk or stretched as necessary to conform to the individual patient's intercomissural distance. For VB stimulation, the initial target, whose coordinates could be directly read from one of the diagrams, was usually the expected area for representation of the contralateral first to third fingers, in the 15.0 mm sagittal plane. From this the desired target can be extrapolated and physiologically confirmed. For PVG, the initial coordinates were 2 mm lateral to the third ventricle wall, 5 mm anterior to PC and at the AC-PC line. Through a burr hole or a 1/8 inch twist drill hole, just in front of the coronal suture and 15 mm from the midline, the electrode was directed to the target. Exploration, from 10 mm above the target to 10 mm below it, at 1 mm (microelectrode) or 2 mm (macroelectrode) steps, was done with macroelectrode stimulation in 2 patients, microelectrode recording and stimulation in 1 patient and both, in 1 patient. Once the desired target was physiologically identified (VB: point where stimulation produces paraesthesiae in the painful area; PVG: point at which stimulation produces pain relief or a pleasant or warm sensation), the monopolar electrodes for chronic stimulation were inserted and fixed to the edge of the bone with a silastic plug. A subgaleal pocket was developed and the extra length of electrode, connector and the percutaneous lead were inserted into it; the extremity of the percutaneous lead was externalized through an adjacent opening and the wounds closed. The whole procedure was done under local anaesthesia. The day after the operation, the patients began a period of trial self-stimulation, connecting the percutaneous lead to an external direct-stimulation device. If after a trial period of, on average, 7 days, the patient found that stimulation provided adequate pain relief, the system was internalized: under general anaesthesia, a pocket was developed in the anterior chest wall to implant the radiofrequency receiver, which was percutaneously connected to the electrode. The patients activated the system by placing an antenna, connected to a transmitter, over the implanted receiver.

RESULTS

Bilateral VB exploration was performed in the four patients. A suitable target was found in all them and the electrodes for chronic stimulation inserted bilaterally. One patient (thoracic cord injury; steady pain only) did not get pain relief and the electrode was removed. The other three patients (75%) enjoyed excellent pain

relief during the trial period and the system was internalized . They continued enjoying excellent pain relief after an average follow-up period of 33.3 months (23-48 months). In one patient (thoracic cord injury; both steady and intermittent pain), pain subsided 3.5 years after the operation, when he stopped using the system; six months later the system got infected due to a traumatic event and was removed . The other two patients (one patient: thoracic cord injury, steady pain only; the other patient: cervical cord injury, both steady and intermittent pain) were still using the system when they were seen in the last follow-up visit.

PVG exploration was performed in three out of these four patients. PVG stimulation produced only nausea and no effect on pain in one patient (cervical cord injury; both steady and intermittent pain) ; an electrode was not inserted. Another patient (thoracic cord injury; both steady and intermittent pain) presented only an unpleasant sensation under PVG stimulation and no electrode was inserted either. Only one patient (thoracic cord injury; steady pain only) had an electrode inserted, despite the fact that during exploration neither effect on pain nor a pleasant or warm sensation was obtained. During the trial period, he did not get adequate pain relief and the electrode was then removed. Summarizing, PVG stimulation was unsuccessful in the three patients.

COMMENTS

It was demonstrated that RVM stimulation produces inhibition of dorsal horn nociceptive neurons by activation of descending inhibitory serotonergic and noradrenergic axons[5,18]. This pathway is localized in both DLF of the spinal cord (Fig 1). Tsubokawa et al.[15] and Willis et al.[19] showed that VB stimulation excites raphe and reticulospinal neurons of the RVM, previously antidromically activated by DLF stimulation (Fig 1). The pathway involved in this excitation is unknown; Gerhart et al suggested that it may be represented by spinothalamic tract collaterals given off to the RVM, antidromicaly activated by VB stimulation. Tsubokawa et al.[17] observed that VB stimulation is effective in inhibiting abnormal hyperactivity in the medullary dorsal horn of cats submitted to retrogasserian rhizotomy and that such inhibition is resistant to naloxone. Gerhart et al.[7] demonstrated that unilateral VB stimulation inhibits the activity of dorsal horn nociceptive neurons, bilaterally, as well as their responses to both noxious and innocuous stimuli (Fig 1). They also showed that these effects could be abolished by a lesion in the spinal cord including both bilateral DLF and the ventral part of the ipsilateral lateral funiculus.

Tsubokawa's hypothesis, based on these experiments, may be summarized as follows: VB stimulation produces pain relief by excitation of the rostroventral medulla, which, in turn, projects descending inhibitory serotonergic and noradrenergic axons through both DLF of the spinal cord to the dorsal horn nociceptive neurons (Fig 1).

Based on the above mentioned findings, one could expect that: unilateral VB stimulation would be effective in producing bilateral pain relief, VB stimulation and PVG-PAG stimulation would be effective for treating the same modalities of pain, since, as shown in Figure 1, PVG-PAG stimulation and VB stimulation[5,18] share the same common final pathway (RVM excitation → dorsal horn inhibition) and that in patients presenting central cord-based pain secondary to complete cord injury, VB stimulation should not work at all.

These assumptions,however, were not borne out by our observations. In fact, quite the opposite was noted: our clinical experience with 62 patients submitted to deep brain stimulation for treating intractable chronic pain syndromes (unpublished data) from June 1978 to July 1991 has demonstrated that VB stimulation is effective only for contralateral pain. It has been demonstrated by Tasker[13], Hosobuchi[8,9] and Levy et al.[10,11] that VB stimulation is effective for treating neural injury pain and PVG-PAG stimulation , to treat nociceptive pain. The present results are in agreement with these data: PVG stimulation was unsuccessful in the three patients of this series. However, Tasker[13] has shown that PVG stimulation is also useful to treat the intermittent and evoked components of the neural injury pain. Two out of three patients of this series presented intermittent pain, but even so, PVG stimulation was unsuccessful.This observation seems to provide clinical confirmation for the experimental data[3,5] showing that PVG stimulation produces analgesia by inhibition of DH nociceptive

neurons through activation of descending pathways located in the DLF: these funiculi were presumably injured in our patients. Finally, our results showed that VB stimulation is useful for treating central cord-based pain in patients with complete cord injury; in fact, 75% (3 out of 4 patients) of the patients in this category enjoyed excellent pain relief.

One could argue that the criteria used to select the patients with complete cord injury were not adequate. One of the patients (thoracic cord injury; steady pain only), however, started complaining of a nociceptive pain in his back, at the site of the spinal injury, sometime after the deep brain stimulation procedure; seventeen months after the first procedure (DBS), a cordectomy, two levels above the original injury, was performed, providing relief of the nociceptive pain, without interfering with the excellent result previously obtained with VB stimulation for his central pain.

Besides this clinical evidence, there is also experimental evidence against Tsubokawa's hypothesis. Benabid et al.[4] were not able to show any inhibition of dorsal horn nociceptive neurons responses to noxious stimuli induced by VB stimulation. Aiko et al.[2], using the14 [C] 2 - deoxyglucose method, studied the effects of VB stimulation on the local cerebral glucose utilization (LCGU) in many central nervous system structures. Alterations in LCGU following electrical stimulation of a separated structure implicate a functional relation between the two structures, through a direct or indirect fiber connection. However, no significant change in LCGU was detected in the spinal dorsal horn, nucleus raphe magnus and nucleus raphe dorsalis. Gerhart et al.[7] demonstrated that, in monkeys, the latency for VB stimulation induced inhibition of dorsal horn neurons in the lumbosacral enlargement is 33.7 ms. Willis et al.[19], working with monkeys also, showed that the latency for VB stimulation excitation of RVM neurons is 35.6 ms and that the latency for antidromic activation of RVM neurons by stimulation of the DLF in an upper lumbar level is 8.2 ms. One can easily see, contrarily to what would be expected from Tsubokawa's hypothesis, that the latency for inhibition of dorsal horn neurons by VB stimulation is less than the sum of the latencies for VB stimulation excitation of RVM neurons and DLF stimulation antidromic excitation of RVM neurons.

In conclusion, there is both clinical and experimental evidence to contest Tsubokawa's hypothesis; if VB stimulation really inhibits dorsal horn neurons, it should play just a partial and not the most important role in the pain relief accomplished by this procedure. Many other hypotheses have been suggested and the authors' opinion is that VB stimulation produces pain relief by activation of a multisynaptic inhibitory pathway to the medial thalamus nociceptive neurons and by modulation of abnormal activity in VB itself.

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