THALAMIC VENTROBASAL STIMULATION FOR PAIN RELIEF

PROBABLE MECHANISMS, PATHWAYS AND NEUROTRANSMITTERS

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SUMMARY - Thalamic ventrobasal (VB) stimulation, first performed by Mazars, in 1961, is a valuable means for treating central and deafferentation pain. The way it acts to achieve pain relief, however, is still a matter of controversy. In this paper, the author examines previously proposed hypotheses and suggests that VB stimulation induces pain relief by activation of a multisynaptic inhibitory pathway to the medial thalamus, in which the dopaminergic nigrostriatal system exerts an important role and by modulation of abnormal activity in VB itself. The multisynaptic pathway involved, as well as the neurotransmitters, are suggested: VB stimulation excites somatosensory cortex through the glutaminergic thalamocortical pathway, which in turn, sends excitatory glutaminergic axons to the motor cortex. The sensorymotor cortex originates the excitatory glutaminergic corticostriatal pathway to the anterior putamen. The anterior putamen sends excitatory peptidergic (substance P) pathways to the globus pallidus internus (striatopallidal pathway) and to the substantia nigra reticulata (striatonigral pathway). The globus pallidus internus inhibits the medial thalamus through the pallidothalamic GABAergic pathway. The substantia nigra reticulata sends inhibitory GABAergic projections to the medial thalamus (nigrothalamic pathway) and excites the substantia nigra compacta. The substantia nigra compacta projects excitatory dopaminergic axons to the striatal neurons (nigrostriatal pathway) with output to the globus pallidus internus and substantia nigra reticulata and so on. Data to support this hypothesis are provided by an extensive review of the literature.

KEY WORDS: pain, analgesia, electrical stimulation, thalamic nuclei, thalamus, cerebral cortex, basal ganglia, neurotransmitters.

Estimulação talâmica ventrobasal para alívio da dor: prováveis mecanismos, vias e neurotransmissores

RESUMO - A estimulação talâmica ventrobasal (VB), primeiramente realizada por Mazars em 1961, é método útil para o tratamento de dor central e dor de deaferentação. A maneira como ela atua para produzir alívio da dor, porém, é ainda questão de controvérsia. Neste estudo, o autor examina as hipóteses anteriormente propostas e sugere que o alívio da dor obtido pela estimulação de VB se deve a dois prováveis mecanismos: (1) Modulação da atividade anormal em VB e (2) Ativação de uma via multisínaptica inibitória para os neurônios nociceptivos do tálamo medial, na qual o sistema dopaminérgico nigroestriatal exerce importante papel. A via multisínaptica envolvida, bem como os neurotransmissores, são sugeridos: a estimulação de VB, através da via tálamo-cortical glutaminérgica, excitaria o córtex somatosensitivo que, por sua vez, excitaria o córtex motor através dos neurotransmissores excitatórios glutamato e aspartato. No córtex sensitivo-motor se originaria a via corticostriatal glutaminérgica excitatória para o putamen anterior, no qual emitiria uma via peptidérgica (substância P) excitatória para o globo palídido interno (via estriatopallidal) e para a substância nigra reticulata (via estriatonigral). O globo palídido interno inibiria o tálamo medial através da via palíd-talâmica gabaérgica. A substância nigra reticulata emitiria projeções gabaérgicas inibitórias para o tálamo medial (via nigrotalâmica) e excitaria a substância nigra compacta. A substância nigra compacta projetaria axônios dopaminérgicos excitatórios para os neurônios

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Thalamic ventrobasal (VB) stimulation seems to be a useful means for treating central (pain secondary to lesion of the central nervous system) and deafferentation (pain secondary to lesion of the peripheral nervous system) pain\(^{12,13,20,25}\). This procedure was first performed by Mazars\(^{16}\), in 1961, and since then many neurosurgeons have adopted the method. The mechanism of pain relief induced by VB stimulation, however, is still unknown. Many hypotheses have been proposed\(^{1,2,6,11,16,23-25,29}\). Unfortunately, none of them seems to completely explain this mechanism.

In this paper, the author examines previously reported hypotheses and proposes that VB stimulation induces pain relief by inhibition of nociceptive neurons of the medial thalamus through a multisynaptic pathway and by modulation of abnormal activity in VB itself. The pathways involved, as well as the neurotransmitters, are suggested. Data to support this hypothesis are provided.

**EXAMINATION OF PREVIOUSLY REPORTED HYPOTHESES**

1. **VB stimulation produces pain relief by antidromic activation of spinothalamic tract collaterals given off to the rostroventral medulla (RVM) raphespinal and reticulospinal neurons, which, in turn, send, respectively, inhibitory serotonergic and noradrenergic axons through both dorsolateral funiculi (DLF) of the spinal cord to the dorsal horn (DH) nociceptive neurons\(^{5,7,11,23-25}\); such inhibition is not affected by administration of naloxone\(^{24}\), but is abolished by a lesion in the spinal cord including both bilateral DLF and the ventral part of the ipsilateral lateral funiculus\(^{11}\).**

   According to this hypothesis, one could expect that VB stimulation would produce bilateral pain relief, VB stimulation would not work in patients with chronic pain harboring complete cord transection and VB and periventricular-periaqueductal gray (PVG-PAG) stimulation would be useful for treating the same modalities of pain, since they presumably share the same common final pathway: RVM excitation $\rightarrow$ DH inhibition\(^{25}\).

   Vilela Filho and Tasker\(^{27}\), however, reviewing their sixteen patients with central cord-based pain (central pain secondary to lesion of the spinal cord) submitted to deep brain stimulation, observed that: A) VB stimulation was effective only for contralateral pain, B) VB stimulation provided excellent pain relief in 3 out of 4 patients harboring complete cord transection, and C) PVG stimulation, performed in 3 out of the 4 patients presenting with complete cord transection, was unsuccessful in all of them, showing that VB and PVG stimulation are not useful for treating the same modalities of pain; this observation seems to provide evidence against the suggestion that VB and PVG stimulation produce pain relief by activation of the same pathway (RVM excitation $\rightarrow$ DH inhibition). Tasker\(^{20}\), Hosobuchi\(^{12}\) and Levy et al.\(^{13}\) have demonstrated that VB stimulation is useful for treating neural injury pain (pain secondary to lesion of the central or peripheral nervous system; it includes both central and deafferentation pain), mainly its steady burning-tingling element, and PVG stimulation, for treating nociceptive pain.

   Besides, there is also experimental evidence against the discussed hypothesis: A) Benabid et al.\(^{4}\) were not able to demonstrate any inhibition of DH nociceptive neurons following VB stimulation; the number of DH cells tested (8 cells), however, was too small, B) Aiko et al.\(^{2}\), using the deoxyglucose method, could not detect any significant change in local glucose utilization in the nucleus raphe magnus and in the spinal dorsal horn following VB stimulation and C) The latency for VB induced inhibition of DH nociceptive neurons -33.7 ms\(^{11,27}\) is less than the sum of the latencies for VB induced excitation of RVM neurons -35.6 ms\(^{27,29}\) and DLF antidromic excitation of RVM neurons -8.2 ms\(^{27,29}\). Despite the evidence against, there is also strong experimental evidence favoring this hypothesis. The clinical data we reported\(^{27}\), however, strongly suggest that if VB stimulation really inhibits DH nociceptive neurons, this mechanism should play at most a partial and not the most important role in the pain relief accomplished by this procedure.
2. VB stimulation, via medial lemniscus, antidromically activates neurons in the dorsal column nucleus, where there is a small but significant number of cells that send axons both to VB and to the spinal cord\textsuperscript{11}. According to Burton and Loewy, quoted by Gerhart\textsuperscript{11}, these neurons seem to regulate the flow of sensory information in spinal systems. This proposal is in agreement with the gate control concept\textsuperscript{4}.

If this hypothesis was correct, VB stimulation would not work in patients with central cord-based pain presenting with complete cord transection. Vilela Filho and Tasker\textsuperscript{27}, however, demonstrated that VB stimulation was effective in 3 out of 4 patients with central cord-based pain harboring complete cord transection. Besides, no increase in local glucose utilization in the dorsal column nucleus and in the spinal cord, following VB stimulation, could be demonstrated by Aiko et al.\textsuperscript{2}.

3. Yezierski et al.\textsuperscript{30} showed that somatosensory cortex stimulation inhibits DH nociceptive neurons responses both to noxious and innocuous stimuli, but mainly to innocuous stimuli and that this inhibition was eliminated or substantially reduced by a lesion in the dorsolateral funiculus of the spinal cord, contralateral to the cortical stimulation site. It is known\textsuperscript{7} that the corticospinal tract originates, in part, from the somatosensory cortex (SI) and that SI also projects to certain subcortical structures, from where the extrapiramidal tracts originate. Yezierski et al.\textsuperscript{30} suggested that the inhibitory effects of SI stimulation on the DH nociceptive neurons could be mediated by both corticospinal and extrapiramidal tracts. Based on these findings, Gerhart et al.\textsuperscript{11} proposed that VB stimulation produces pain relief by activation of these corticofugal pathways.

Again, if this hypothesis was correct, VB stimulation would not work in patients with central cord-based pain harboring complete cord transection; Vilela Filho and Tasker\textsuperscript{27}, however, showed that VB stimulation was effective in 75\% of their patients classified in this category.

There is also experimental evidence against this hypothesis: A) Aiko et al.\textsuperscript{2} demonstrated increase in local glucose utilization in SI, but not in the DH, following VB stimulation, B) SI stimulation inhibits preferentially DH nociceptive neurons responses to innocuous stimuli while VB stimulation has no preferential effect, although DH nociceptive cells responses to C fiber volleys are reduced to a greater extent than their responses to A fiber volleys\textsuperscript{11,30}, C) SI stimulation ipsilateral to an spinothalamic tract neuron produces only weak inhibitory effects, while ipsilateral VB stimulation usually causes a powerful inhibition\textsuperscript{11} and D) Inhibition of the responses of spinothalamic cells to noxious stimuli following VB stimulation is observed even when SI stimulation fails to inhibit the responses of the same cells to such stimuli\textsuperscript{11}.

4. Adams et al.\textsuperscript{1} suggested that VB stimulation activates inhibitory fibers arising from the parietal cortex to the thalamus and spinal cord.

If such a simple thalamocortical-corticothalamic circuit for inhibition is accepted, the expected latency for inhibition would be too short. Benabid et al.\textsuperscript{6}, however, showed that the latency for VB inhibition of medial thalamus nociceptive neurons is very long: 100-200 ms. So, VB stimulation inhibition of MT via this circuit is improbable. Besides, according to Steriade\textsuperscript{18}, corticothalamic fibers are, without exception, excitatory.

The possibility of VB-induced pain relief by inhibition of nociceptive neurons at the spinal cord level was already contested.

5. Benabid et al.\textsuperscript{6} demonstrated that VB stimulation inhibits nociceptive neurons in the MT and suggested, considering the absence of labelled cells in VB following horseradish peroxidase administration in the MT, the long latency for inhibition and the lack of influence of naloxone administration, that this inhibition could be mediated by a multisynaptic, nonopioid pathway.

This looks like an interesting hypothesis. It is supported by Aiko's results\textsuperscript{2}, showing an increase of local cerebral glucose utilization (LCGU) in the MT following VB stimulation. The multisynaptic pathway involved, however, was not established.

6. Mazars\textsuperscript{16} proposed that VB stimulation would compensate for the lack of sensory input reaching the thalamocortical circuit in patients with neural injury pain.

This hypothesis is supported by Aiko's\textsuperscript{2} findings (increase of LCGU in VB and in the somatosensory cortex following VB stimulation). However, it presumes an excitatory effect of VB stimulation and there seems to be a general agreement that the final effect of VB stimulation is inhibitory. Besides, bursting cells (neurons with spontaneous discharge, interpreted as deafferented cells and commonly linked to the genesis of central and deafferentation pain) have been detected in VB by Tasker et al.\textsuperscript{20}; they could be responsible for hyperactivity, instead of hypoactivity, in the thalamocortical circuit.
7. There is increasing evidence that the dopaminergic nigrostriatal system exerts a potential influence on pain inhibition by VB stimulation. Lin et al.\(^1\) demonstrated that stimulation of substantia nigra (SN) and striatum in rats induces pain relief. Tsukokawa et al.\(^2\) and Hosobuchi\(^3\) observed that administration of L-dopa reverts or inhibits tolerance to chronic VB stimulation. Aiko et al.\(^4\) detected an increase of LCGU in the SN following VB stimulation.

This is another interesting possibility, but the way the dopaminergic nigrostriatal system affects pain relief induced by VB stimulation was not elucidated.

**PRESENT HYPOTHESIS**

VB stimulation produces pain relief by activation of a multisynaptic inhibitory pathway to the nociceptive neurons of the medial thalamus and by modulation of abnormal activity in VB itself through intrinsic circuits; both mechanisms might act simultaneously (Fig 1). The following are the multisynaptic pathway and the neurotransmitters that this author suggests: VB stimulation excites the somatosensory cortex through the glutaminergic thalamocortical pathway, which in turn excites the motor cortex using the excitatory neurotransmitters glutamate and aspartate. Both somatosensory and motor cortex send excitatory glutaminergic projections (corticostriatal pathway) to the anterior putamen. The anterior putamen projects excitatory peptidergic (substance P) axons to the globus pallidus internus (GPI) and substantia nigra reticulata (SNR) through the striatopallidal and striatonigral pathways, respectively. The GPI and SNR inhibit the medial thalamus through, respectively, the GABAergic pallidothalamic and nigrothalamic pathways. The SNR excites the substantia nigra compacta (SNC), which, in turn, sends excitatory dopaminergic efferents (nigrostriatal pathway) to the part of striatum with output to the GPI and SNR and so on (Fig 1).

**SUPPORTING DATA TO THE PRESENT HYPOTHESIS**

Bursting cells are neurons with spontaneous discharge interpreted as deafferented cells and have commonly been linked to neural injury pain\(^1\)\(^2\). They were recently detected in the medial thalamus (MT) of patients with neural injury pain (NIP) by Rinaldi et al.\(^1\). According to Tasker\(^1\)\(^2\), electrical stimulation of the MT in “normal” patients (patients without NIP) does not evoke any conscious response; in patients with neural injury pain, however, it may evoke a non-somatotopographically organized contralateral burning or pain, mimicking the patient’s own pain. Among MT afferents there is the reticulothalamic tract\(^7\) whose stimulation at the upper brainstem, in patients with NIP, induces a response similar to that produced by stimulation of the MT\(^1\)\(^2\). Medial mesencephalic tractotomy and medial thalamotomy are not infrequently valuable procedures for treating neural injury pain\(^2\).

For all these reasons, the MT seems to be, in someway, involved in the genesis of neural injury pain. Modulation of its abnormal activity could be expected to relieve NIP.

Ishijima, quoted by Timo-Iaria\(^2\), demonstrated that stimulation of the sciatic nerve or spinothalamic tract in cats produces evoked potentials both in the MT and VB and that VB stimulation

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**Fig 1.** Mechanism of pain relief by thalamic ventrobasal stimulation: probable pathways and neurotransmitters. Legend: excitation = - - - - ; inhibition = - - - o.
inhibits the evoked potentials in the MT produced by stimulation of the spinothalamic tract and sciatic nerve.

Tsubokawa and Moriyasu\textsuperscript{22} identified nociceptive neurons in the MT using peripheral noxious stimuli both in a monkey model and in humans with nociceptive pain during operation. They showed that VB stimulation inhibited both medial thalamus nociceptive neurons spontaneous discharge and their responses to peripheral noxious stimuli.

Benabid et al.\textsuperscript{6} demonstrated a similar effect of VB stimulation on medial thalamus nociceptive neurons of rats and that this response was not influenced by administration of naloxone. Trying to discover a monosynaptic pathway between VB and MT, they injected horseradish peroxidase in the last structure; no labelled cells, however, could be found in VB. On the other hand, the latency for VB induced inhibition of MT was too long (100-200 ms), suggesting a multisynaptic connection between them.

Unfortunately, Tsubokawa's\textsuperscript{22} and Benabid's\textsuperscript{6} models concerned only "normal" individuals and Rinaldi's work\textsuperscript{17} in patients with NIP just demonstrated the presence of bursting cells in the MT, no attempt being made to show VB stimulation effect on these cells.

Bursting cells have also been identified in other sites: Tasker\textsuperscript{20} found them in VB and Loeser\textsuperscript{17,20}, in the dorsal horn. Modulation of their activity is these sites could also be expected to produce pain relief.

Aiko et al.\textsuperscript{2} studied the effects of VB stimulation on the local cerebral glucose utilization (LCGU) in many structures of the nervous system. A significant increase in LCGU was observed in the following ipsilateral structures: sensorymotor cortex, substantia nigra pars reticulata (SNR) and compacta (SNC), MT and in VB itself. Since alterations in LCGU of certain structures determined by electrical stimulation of other structure implicate a functional relationship between them either by direct or indirect fiber connection, one might assume that all these structures are relays of a multisynaptic pathway involved in VB induced inhibition of MT (lack of increase in LCGU, however, does not necessarily prove the absence of functional neural pathways). Besides, it is known that VB stimulation induces only contralateral pain relief\textsuperscript{27} and that all structures showing increase in LCGU were ipsilateral to VB.

In fact, electrical stimulation of all these structures may produce pain relief.

Tsubokawa et al.\textsuperscript{26} have been successfully using motor cortex stimulation for treating central brain-based pain (central pain secondary to lesion of the brain) and Lin et al.\textsuperscript{14} demonstrated that SN and striatum stimulation induce relief for pain. Yezierski et al.\textsuperscript{30}, stimulating somatosensory cortex and Andy\textsuperscript{3}, stimulating MT, were also able to accomplish pain relief.

Anatomical connections between these structures are also established.

It is long known that VB neurons send their axons to the somatosensory cortex (thalamocortical pathway) through the posterior limb of the internal capsule\textsuperscript{8}. The neurotransmitters involved in this pathway are, apparently, the excitatory amino acids glutamate and aspartate\textsuperscript{18}. Abundant connections between somatosensory and motor cortex have also been established. According to Martin and Jessell\textsuperscript{15}, pyramidal neurons in layers 2 and 3 of the somatosensory cortex, which receive thalamic input, make reciprocal association connections with neurons of the motor cortex, using the excitatory glutamate or aspartate as neurotransmitters.

Both somatosensory and motor cortex project to the anterior part of the putamen\textsuperscript{28}. The head of caudate receives inputs from the association areas of the cortex and the posterior striatum receives inputs from widespread areas of the cortex\textsuperscript{28}. The neurotransmitter used by the corticostriatal pathway is the excitatory amino acid glutamate\textsuperscript{28}. The striatum projects to the SNR through the striatonigral
pathway and to the globus pallidus, through the striatopallidal pathway\textsuperscript{9,28}. The main neurotransmitters found in these pathways are the excitatory substance P and the inhibitory GABA\textsuperscript{28}.

Barasi and Pay\textsuperscript{4} recorded the spontaneous activity of a number of cells in the SN. Half of them were responsive to noxious stimulation. 80\% of the striatal afferents influenced nociceptive neurons in the SN. Two striatonigral pathways have been proposed: an excitatory peptidergic (substance P) pathway, derived mainly from the anterior striatum and an inhibitory GABAergic pathway, derived mainly from the posterior striatum.

The SNR and SNC are interconnected\textsuperscript{28}. The SNR projects inhibitory GABAergic axons to the MT through the nigrothalamic pathway\textsuperscript{9,28}. The SNC sends dopaminergic projections to the striatum through the nigrostriatal pathway\textsuperscript{9,28}. There is considerable controversy regarding the effect of dopamine on striatal output. Recent evidence\textsuperscript{28} suggests that this effect seems to depend on where the striatal neurons terminate: excitatory effect may predominate for output to globus pallidus internus (GPI) and SNR, while inhibitory effect predominates for output to globus pallidus externus (GPE).

Tsubokawa et al.\textsuperscript{23} and Hosobushi\textsuperscript{12} demonstrated that the tolerance induced by continued VB stimulation could be prevented or reverted by administration of L-Dopa. This very interesting finding seems to point to the importance of the dopaminergic pathways for the pain relief obtained by VB stimulation.

The GPI, through the pallidothalamic pathway, sends inhibitory GABAergic projections to the medial thalamus\textsuperscript{8,9,28}.

**CONCLUSION**

Many hypotheses have been proposed trying to explain the mechanism by which VB stimulation produces pain relief. Evidence may be raised against most of them. On the other hand, those suggesting the inhibition of medial thalamus nociceptive neurons and the influence of the nigrostriatal system as possible mechanisms for pain relief look very promising. This author agrees with these two possibilities and suggests the pathways probably involved, as well as the neurotransmitters. The proposal here reported is supported by an extensive review of the literature and seems to adequately correlate and explain the data presently available.

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