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Journal of General Medicine and Clinical Practice

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Review Article

Synchronizing Mechanisms of The Thalamus

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Received date: February 01, 2025; Accepted date: February 10, 2025; Published date: February 18, 2025

Citation: Bon E.I., Maksimovich N.Ye., Rishkel A.A., (2025), Synchronizing Mechanisms of The Thalamus, *J. General Medicine and Clinical Practice,* 8(2); **DOI:10.31579/2639-4162/252**

Abstract

The question of the source of various forms of rhythmic activity is important for understanding the intracentral relationships as well as the functional role of brain structures where this type of activity is observed. Furthermore, elucidating the mechanisms of synchronizing activity may be a crucial factor in understanding fundamental brain states such as sleep and wakefulness, arousal response, orienting reflex, etc. The fact that spindle-shaped and "bursting" barbiturate activity at a frequency of 8-12 Hz occurs synchronously in the cerebral cortex and nonspecific thalamic nuclei has led to the suggestion that the primary source of their generation is the thalamus (nonspecific nuclei). This assumption was strengthened after it was established that removal of the cortex does not suppress "bursting" activity in the thalamus in both unanesthetized animals and under barbiturate anesthesia. Similar data were obtained from preparations of the "isolated thalamus."

Kew Words: brain; thalamus; neurons

Introduction

The question of the source of various forms of rhythmic activity is important for understanding the intracentral relationships as well as the functional role of brain structures where this type of activity is observed. Furthermore, elucidating the mechanisms of synchronizing activity may be a crucial factor in understanding fundamental brain states such as sleep and wakefulness, arousal response, orienting reflex, etc. The fact that spindle-shaped and "bursting" barbiturate activity at a frequency of 8-12 Hz occurs synchronously in the cerebral cortex and nonspecific thalamic nuclei has led to the suggestion that the primary source of their generation is the thalamus (nonspecific nuclei) [2-10]. This assumption was strengthened after it was established that removal of the cortex does not suppress "bursting" activity in the thalamus in both unanesthetized animals and under barbiturate anesthesia. Similar data were obtained from preparations of the "isolated thalamus." Finally, after partial destruction of thalamic structures or transection of thalamocortical pathways, one can observe the disappearance of any forms of rhythmic brain activity with a frequency corresponding to the alpha rhythm. Thus, the concept of the thalamus as a pacemaker of "bursting" electrical activity in the brain has been established. However, this is not the only viewpoint, and it is not shared by several authors who believe that "bursting" electrical activity, arising in the thalamus, is controlled by the cerebral cortex [4]. This conclusion is based on the fact that complete decortication (not only of the convexital part but also of the basal regions of the cortex) blocks "bursting" activity in the thalamus [3-8].

Engagement Response and Enhancement Response

The most important facts regarding the role of thalamic nuclei in generating rhythmic brain activity have been obtained from studies on the engagement response and enhancement response. These are the primary types of responses that occur during low-frequency (5-15 impulses/sec) stimulation of nonspecific (engagement response) or specific (enhancement response) thalamic nuclei [5-10].

The engagement response was first described by Morrison and Dempsey during low-frequency stimulation of the medial group of thalamic nuclei. The response, characterized by an increase and subsequent decrease in amplitude with initially negative waves, was recorded from extensive areas of the cortex; however, it was most pronounced in certain zones (orbitofrontal, motor, parietal, and limbic). Morrison and Dempsey, followed by other researchers, noted similarities between the potentials of the engagement response and those of background "bursting" activity. Consequently, a conclusion was drawn about the unified mechanisms and common source of these forms of activity [20-24].

Subsequently, in the works of Velasco and Lindley, as well as in a number of other studies, these same questions were examined from a different perspective. When investigating the role of various cortical fields in the genesis of bursting activity, the authors concluded that there is a close functional connection between the nonspecific thalamic nuclei and the orbitofrontal cortex. It was found that stimulation of the intralaminar thalamic nuclei induces a rhythmic reaction in the orbitofrontal cortex that fully corresponds to the potentials of the enhancement response previously observed only during stimulation of relay thalamic nuclei [11-16]. In contrast, a clear engagement response was observed in primary sensory areas. Removal of the orbitofrontal cortex or the disruption of fiber bundles running from the orbitofrontal cortex to the nonspecific thalamic nuclei within the lower thalamic peduncle suppresses bursting background activity

and potentials of the engagement response. Suppression of bursting activity and recruiting effects in the cerebral cortex was observed after transection of the medial bundle of the forebrain if the transection was performed rostrally to the exit of the lower thalamic peduncle. All these facts led to the conclusion that the orbitofrontal cortex controls the activity of nonspecific (primarily medial group) thalamic nuclei, which, in turn, ensure synchronization of EEG, serving as a pacemaker for bursting electrical activity in the brain [17].

At the same time, according to Anderson et al., destruction of the orbitofrontal cortex may not be as significant for ensuring bursting activity produced by thalamic influences as Velasco and Lindley believed. The transmission of influences from the thalamus that induce bursting activity in the cerebral cortex occurs not only from nonspecific nuclei but predominantly through fibers from relay thalamic nuclei. Subsequent experimental studies aimed at clarifying this issue have not been able to completely exclude the role of the orbitofrontal cortex in generating synchronized activity by medial thalamic nuclei [18].

Mechanisms Of Thalamic Synchronized Activity

The most common viewpoint on the mechanisms of thalamic synchronization is based on the hypothesis by Andersen and Eccles regarding feedback inhibition through an interneuron system, which has already been mentioned. As shown by Andersen et al., in response to a single peripheral stimulation, relay neurons in the ventrobasal complex do not generate just one complex of excitatory postsynaptic potentials (EPSPs) and inhibitory postsynaptic potentials (IPSPs), but rather a series of them, occurring at a frequency of about 8-12 impulses per second. Similar oscillations of membrane potential in neurons of nearly all major thalamic nuclei are observed during explosive background activity provoked by the administration of barbiturates. With intracellular recordings from neurons, it can be seen that at the beginning of each spindle burst, a series of IPSPs occurs, increasing in amplitude as the spindle develops. The IPSPs last about 120 ms, corresponding to a rhythm of 8 impulses per second [15-22].

In a series of works conducted by Purpura, similar phenomena were observed during engagement and enhancement responses triggered by stimulation of the medial group of nuclei. During the engagement response induced by stimulation of the medial thalamic nuclei, the sequence of EPSPs and IPSPs was observed not only in the cerebral cortex but also in other thalamic nuclei (intralaminar nuclei). The very first stimulus applied to the medial part of the thalamus induces a long-lasting and powerful IPSP in relay and nonspecific nuclei neurons, with its amplitude increasing as stimulation continues. The sequence of EPSPs and IPSPs is accompanied by neuronal discharges that are timed with the development of the EPSP. However, in some neurons, this sequence is not accompanied by discharges because the IPSP increases to such an extent that, when summed with it, the EPSP does not reach the critical level of depolarization [10-14].

Rhythmic activity can be viewed as a phenomenon in which different neurons within a nucleus participate to varying degrees [16].

There is no doubt that inhibitory interneurons are crucial for generating significant IPSPs in most thalamic neurons during the synchronization process. These interneurons may be inhibitory for certain relay cells within the nucleus and possibly excitatory and inhibitory for other relay cells and interneurons. The same authors suggested that inhibition in the thalamus may have a presynaptic nature. This suggestion was made partly due to difficulties in locating inhibitory interneurons. In any case, interneurons whose discharge durations correspond to the duration of synchronized inhibitory postsynaptic potentials (IPSPs) have not been found in close proximity to the neurons where such IPSPs were recorded, despite several indications [13-22].

The Role of The Reticular Nucleus in Thalamic Synchronized Activity

In addition to the feedback inhibition that can be carried out by short-axon interneurons functioning within the nucleus, there may be inhibition provided by frequency discharges coinciding with the excitatory postsynaptic potentials (EPSPs) in relay neurons, as observed in the intralaminar nuclei [14-21].

The reticular nucleus of the thalamus has gained significant importance in the mechanisms of thalamic synchronization after Sheibel suggested that neurons whose axons project caudally and distribute to relay and nonspecific nuclei may produce long-lasting and widespread EPSPs through feedback inhibition. All thalamocortical fibers passing through the reticular nucleus give off collaterals to the dendritic network of this nucleus [17-20].

The close structural and functional similarity between the rostral pole of the reticular nucleus and the rostromedial part of the intralaminar nuclei suggests that the latter may also participate in the mechanisms of thalamic synchronization, similar to the reticular nucleus [15-23].

Electrophysiologic ally, it has been shown that high-frequency discharges can occur in neurons of the reticular nucleus during intervals between phases of rhythmic activity in relay neurons. Furthermore, when stimulating fibers in the internal capsule, a typical sequence of EPSPs—EPSPs or EPSPs—spike—EPSPs occurs in the neurons of the intralaminar nuclei, while at the same time, high-frequency discharges are observed in cells of the reticular nucleus during this period, which is seen both with single stimulation and with low-frequency stimulation (8 impulses/second), provoking a recruiting effect. Finally, another observation allows us to consider the role of the reticular nucleus in the mechanisms of synchronization with attention. Axons from cells in the reticular nucleus directed toward neurons in the intralaminar nuclei make contacts not with a single neuron but with their chain lying in a rostrocaudal direction. It is possible that the sequential involvement of neurons in this chain in inhibition may explain the phases of increase and decrease in response potentials associated with spindle and alpha-like activity [15-20].

Thus, by providing feedback inhibition to thalamic nucleus neurons, the reticular nucleus may act as a sort of frequency filter, allowing only low-frequency oscillations to pass to the cerebral cortex. However, it should be noted that in the reticular nucleus, which is the last station of the nonspecific thalamic system on its way to the cerebral cortex, processes that begin in the nonspecific thalamic nuclei come to an end. These mechanisms are demonstrated in neurons of the intralaminar nuclei. Monosynaptic excitation of relay neurons in the intralaminar nuclei during stimulation of cerebellar-thalamic pathways (connecting peduncles) is completely blocked when long-lasting EPSPs occur and is suppressed for some time after cessation of low-frequency stimulation (7 impulses/second) of the medial thalamic nuclei. Such "filtering" of afferent signals at the level of the thalamic relay nucleus reflects one aspect of the modulatory activity of nonspecific thalamic nuclei, which is quite similar to the activity of other nuclei (and may possibly be carried out through this nucleus) [9-11].

The Relationship Between Thalamic Synchronized Activity and Reticular Influences

The study of reticular influences on thalamic neurons helps to understand the mechanism of desynchronization of electrical activity in the brain. When examining the effects of peripheral stimuli that induce arousal on the conduction of afferent waves through thalamic relay nuclei, it was found that its primary form consists of facilitating responses to a modality-specific stimulus for that relay. Facilitation is also observed when stimulating the mesencephalic reticular formation. It should be noted that in some neurons of the Ō region, which respond to light flashes with physical reactions accompanied by inhibitory pauses, the addition of an auditory stimulus that

induces arousal leads to the "filling" of the inhibitory pause. In this regard, it is suggested that the enhancement of conduction through relay nuclei during reticular activation is due to two factors: inhibition of inhibitory interneurons and depolarization of relay thalamocortical neurons. This is supported by the following facts: first, the activity induced in interneurons is suppressed during high-frequency stimulation of the reticular formation; second, in relay thalamocortical neurons of the C̄ region, such stimulation results in suppression of spontaneous and evoked postsynaptic potentials (PSPs) [5-9].

It is noteworthy that low- and high-frequency stimulation of nonspecific thalamic nuclei has opposing effects on synaptic processes in other thalamic nuclei (both nonspecific and relay). In particular, stimulation of the medial part of the thalamus at a frequency of 7 impulses/second induces a sequence of excitatory postsynaptic potentials (EPSPs) followed by PSPs in neurons of the ventromedial thalamus, which are eliminated by high-frequency stimulation (60 impulses/second) and replaced by summating EPSPs that lead to significant depolarization of the neuron's membrane [10-13].

During high-frequency stimulation of the reticular formation in the pons, against the background of an engagement response (stimulation of medial thalamic nuclei at a frequency of 7 impulses/second), neurons in the Ū region show blocking or reduction of synchronizing PSPs and increased excitability of these neurons. As a result of blocking PSPs, synaptic transmission in relay neurons of the Ū region from cerebellofugal influences is restored, and even synaptic signaling in the thalamocortical system is enhanced. Subsequently, similar results have been obtained in other thalamic nuclei by other researchers [12].

Analyzing the data presented above, two positions are highlighted: first, the reduction or blocking of synchronizing PSPs is a necessary condition for the manifestation of thalamocortical desynchronization; second, the enhancement of excitatory synaptic signaling in thalamic neurons accompanies this "inhibition of inhibition."

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DOI:10.31579/2639-4162/252