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Some Characteristics of Neurons in the Reticular Nucleus of the Thalamus (Preliminary Data)

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Abstract

Our general understanding of the function of neurons is that dendrites receive information that is relayed to the axon, where action potentials are initiated and propagated to eventually trigger neurotransmitter release at synaptic terminals. Although for a number of neuron types in the mammalian brain, many neuron types do not follow this classical polarity pattern. In fact, dendrites may be the site of action potentials initiation and propagation. It should be noted that convincing evidence has been obtained for the existence of dendritic action potentials in hippocampal and neocortical neurons. With regard to the dendrite potentials of thalamic neurons in general and specifically the reticular nucleus of the thalamus, it has not yet been reported. The results of this study demonstrate, for the first time, that generation of spike potentials of different amplitudes was observed in the activity of the thalamic reticular nucleus neurons. The generation of one action potential does not interfere with the generation of another, and a spike potential of smaller amplitude can occur at the ascending or descending phase of the spike potential of large amplitude. It can be argued that the spike potentials of lower amplitudes arising in the thalamic reticular nucleus neuron are of dendrite origin. Given both the strategic position and the functional purpose of the TRN, it can be assumed that the neurons of this structure must each time be discharged with spike potentials in order to carry out their modulating effect on other areas of the nervous system of the brain without leakage.

Keywords

Thalamus, Neuron, Dendrite Potentials, Cat

1. Introduction

The study of integrative processes taking place in different structures and at different levels of the brain is important for elucidating the function of individual brain formations and their role in its integral activity. The reticular system, which includes the formations of the brain stem and diencephalon, carries a certain load both in the regulation of the activity of other parts of the central nervous system, and in its activity as a whole [1].

Among the reticular formations, the thalamic reticular nucleus (TRN) deserves special attention, which occupies an exclusive strategic location between the neocortex and other sub-cortical structures of the brain [2]. The TRN forms a shell around the dorsal thalamus and consists of GABA-ergic neurons, which provide a strong inhibitory input on thalamic relay cells [3]. All axons connecting thalamic nuclei and cortical areas in both directions send collaterals to TRN neurons. TRN neurons are activated by thalamo-cortical and cortico-thalamic glutamatergic axons and axonal collaterals of thalamic or cortical cells, providing a feedback or feed-forward inhibition, respectively, for thalamic relay neurons [4]. Based on these electrophysiological and anatomical findings, a hypothesis was formulated that the TRN could act as a "band-pass filter" in control of various thalamic inputs and, that TRN may be involved in modulating the conduction of various afferent impulses.

Experiments conducted by us in previous years have shown the role of TRN in the normal and pathological activity of the brain.

In particular: 1) Stimulation of the TRN evoked monosynaptic inhibitory postsynaptic potentials (IPSPs) in the thalamic relay neurons [5]. It can be seen from the figure, that the single stimulation of TRN led to the appearance of IPSPs of varied duration (80 to 400 ms) and with different latent periods (1 - 2 to 12 ms) in dorsal lateral geniculate body (DLG) neurons. Similar results were obtained when unit activity was recorded in VL. The IPSP arising in VL and LGB neurons in response to single stimulation of TRN was sometimes repeated several times and became, as it was, rhythmic in character, **Figure 1**.

2) The TRN neurons, during the hippocampal generalized convulsive seizures, were classified into one of the three types, according to their oscillatory properties. Type 1 neurons (23 units out of 120; 19.1%) were those, in which the spontaneous high-frequency burst discharges density dropped after the onset of the hippocampal evoked epileptic activity. Type 2 neurons (45 units out of 120; 37.5%) were those, in which the activity was significantly enhanced during the silence period of the clonic phases and at the end of seizure episodes. Type 3 neurons (52 units out of 120; 43.3%) were those, in which discharges were in a close time relation with the EEG self-sustained seizure activity after the cessation of the convulsive activity simultaneous cessation of the TRN neurons seizure discharges was observed [5]. The activity of TRN neurons was significantly enhanced during the silence within the seizure episodes, **Figure 2**.

3) The effect of TRN stimulation on responsiveness of nociceptive neurons

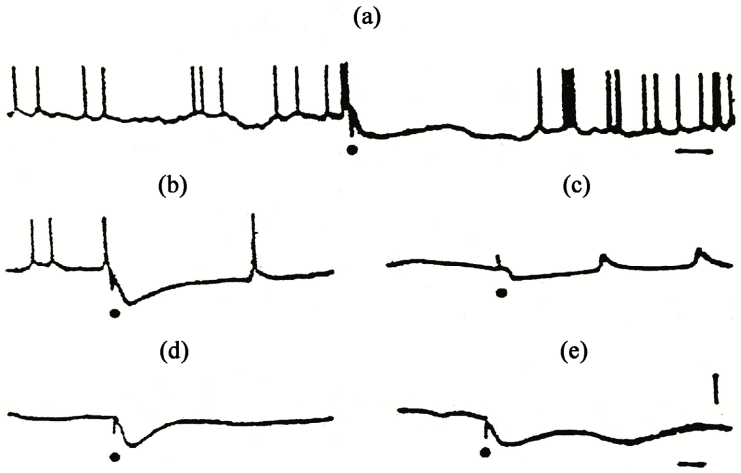

Figure 1. Effects of stimulation of TRN on unit activity in thalamic relay nuclei. (a), (c) lateral geniculate body; (b), (d), ventrolateral nucleus. Dots indicate times of TRN stimulation. Calibration: (a), 100 msec; (b) - (e), 3 msec; 20 mV. From Nanobashvili Z. *et al.* (2012).

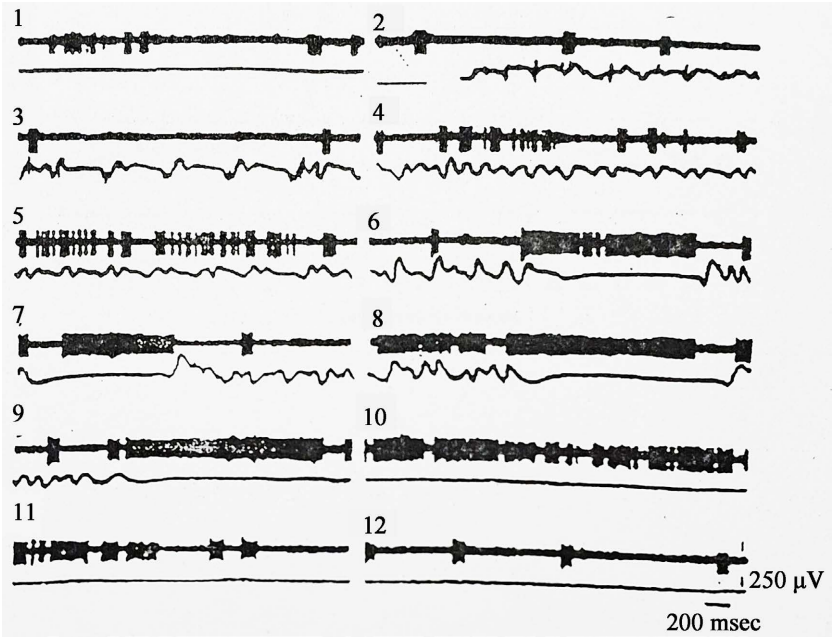

Figure 2. Relationships between the neocortical (lower traces) epileptic activity and spike discharges of the TRN neuron (upper traces) following the high-frequency electrical stimulation (2) of hippocampus (50 μA, 60 Hz, 10 sec). 1, spontaneous activity; 2 - 9, evoked seizure discharges; 9 - 12, cessation of epileptic activity, from Nanobashvili Z. *et al.* (2012).

within the ventral posteromedial thalamic nucleus (VPM) have been studied [6]. **Figure 3** shows changes in responsiveness of the thalamic VPM nucleus neurons to a nociceptive stimulation at the preliminary stimulation of the TRN. It is seen in the Figure that the TRN stimulation significantly suppresses VPM neuron's responsiveness not only to tooth pulp stimulation, but also the spontaneous activity of neurons.

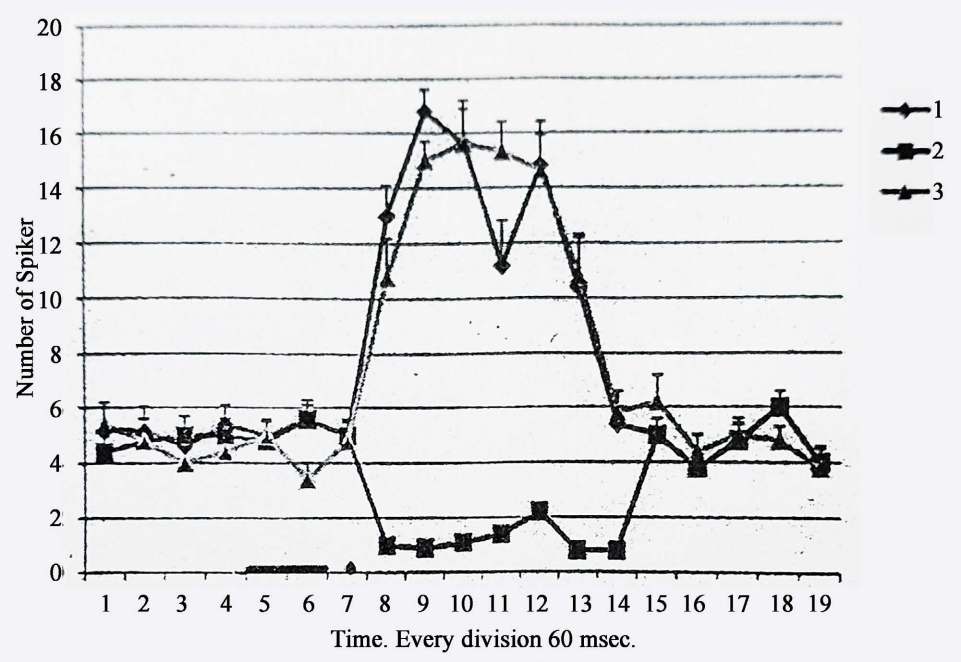

Figure 3. The effect of TRN stimulation (2) on responsiveness of nociceptive neurons within the thalamic VPM nucleus (1, 2). The bold line on the abscess indicates irritation of TRN (50 Hz, 50 μA), and the dot indicates pain stimulation (60 μA). From Nanobashvili Z. *et al.* (2021).

4) Recently, we showed that the development of kindling induced by hippocampal stimulation can be blocked by simultaneous stimulation of the TRN. The latter stimulation was capable of blocking generalization of the seizures when two different paradigms of kindling were used. When discussing other possibilities, we postulated that blocking of the seizure reactions induced by stimulation of the thalamic TRN can result from potentiation of the activity of GABA-ergic inhibitory neurons of the latter nucleus [7]. Intra- or quasi-intracellular recordings from relay neurons of the ventral lateral thalamic nucleus (VL) showed that IPSPs evoked in these neurons by single stimulations of the TRN are significantly facilitated both in the course of conditioning tetanically stimulation of the above nucleus by high-frequency series and for a rather long time after such stimulation. Single stimulation of the TRN with a near-threshold intensity evoked low amplitude IPSPs in the studied neurons, and their background spike activity was suppressed for 200 to 400 msec (**Figure 4(a)**) Conditioning tetanic stimulation of the TRN was performed by application of 10 series of stimuli (10 stimuli in each; 50 Hz; interseries intervals 10 sec). Such high frequency series evoked IPSPs, whose amplitude was several times greater than that at single pulse TRN stimulations (**Figure 4(b)**). After this, the TRN-induced effects were tested by single stimulations of this nucleus. In this case, single pulses evoked IPSPs also with an amplitude several times higher than that before conditioning tetanic stimulation (**Figure 4(c)**). Potentiation of the TRN-induced IPSPs on VL neurons was preserved for 10 - 25 min after termination of rhythmic stimulation of the TRN.

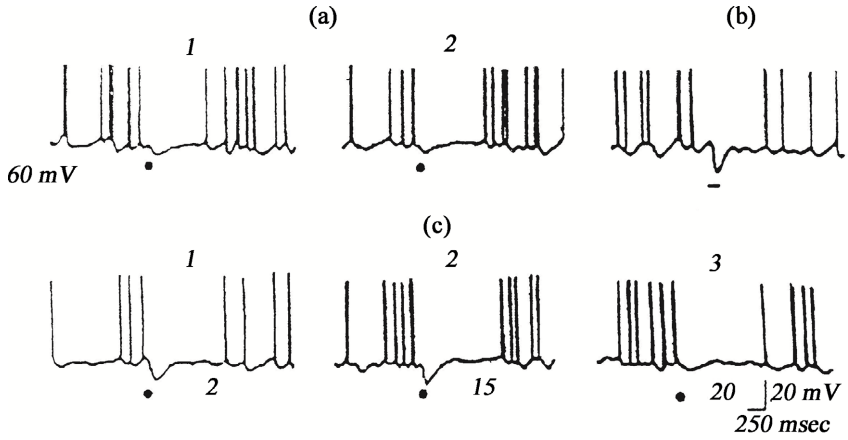

Figure 4. Potentiation of inhibitory postsynaptic effects in a neuron of the VL of the thalamus of the cat after rhythmic stimulation of the TRN. Intracelullar recording from the VL neuron; the membrane potential, mV, is shown at the left. (a), 1, 2) Effects of single stimulations of the TRN; (b) Effect of the 10th stimulation of the TRN by a series of 10 stimuli of the same intensity as in panel A, applied at a 50 sec - 1 frequency; interseries intervals were 10 sec; (c), 1 - 3) Effects of single stimulations of the TRN with the same intensity applied with different intervals (shown below the traces, min) after termination of rhythmic stimulations. From Nanobashvili Z. *et al.* (2005).

It also turned out that: 1) TRN plays an important role in organizing the earliest connections between the neocortex and the thalamus [8]. 2) In persons with chronic neuropathic pain, there is a significant decrease in the volume of TRN [9]. 3) The role of TRN in cognitive impairment in Alzheimer's disease is assumed [10]. 4) Different subtypes of TRN neurons contribute differently to the processing of sustained nociception induced by formalin in freely moving mice [11].

Based on the above, some characteristics of neurons in the TRN would be studied.

2. Methods

Acute experiments were carried out on adult cats (n = 8) weighing 2.5 to 3.0 kg. Housing of, surgical manipulations with, and euthanasia of the animals were carried out in accordance with the rules and standards accepted by the scientific community of the European Union, legislation of Georgia, and the Committee on the care and use of animals in the Center of Life Sciences of Georgia. Instructions of the administration of the National Institutes of Health (Bethesda, USA) on the care and use of laboratory animals (NIH Publication No. 88-2959) were also taken into account.

According to coordinates of the atlas of Reinoso-Suarez F., [12], bipolar steel electrodes were inserted under ether anesthesia into the ventral-lateral thalamic nucleus (VL). The electrical stimulation was determined with a stimulator (S88, Grass, Quincy, MA, U.S.A.).

After insertion of the electrodes the administration of ether was stopped and the animals were immobilized by intravenous injection of tubocurarine and arti-

ficially ventilated. The experiments began 1.0 - 1.5 h after administration of ether had ceased. Small doses of pentobarbital (5 to 8 mg/kg) were additionally injected when necessary. All wound surfaces were periodically treated with a 2% lidocaine solution.

The activity of TRN neurons was recorded with glass microelectrodes. The parts of the lateral and suprasylvian gyri were removed by suction, the lateral ventricle was opened and caudal nucleus and hippocampal fimbria were exposed, which serves as reference points for microelectrode insertion into the TRN. Micropipettes filled with 3 M potassium citrate solution served as glass microelectrodes. The diameter of the microelectrode tips did not exceed 1.5 μm, and the resistance was 15 - 35 MΩ.

After the end of the experiment, the animals were deeply anesthetized. Sites of localization of the tips of the electrodes were coagulated (constant current 2 to 3 μA was passed during 1 min). The brain was taken off and fixed in a 4% paraformaldehyde solution on phosphate buffer. Localization of the electrode tips was verified in frontal slices.

3. Results and Discussion

Of all intracellular records (n = 23) of the activity TRN neurons in three cases, we observed the following event: in the spontaneous activity of TRN neurons, generation of the potentials of different amplitudes was observed, representing a very uniform group of phenomena (Figure 5).

Based on their amplitude and the occurrence of discharges in a given cell, two repetitive types of potentials can be distinguished, large and smaller (shown by arrows) amplitude. On Figure 5 it can be seen that each time both potentials

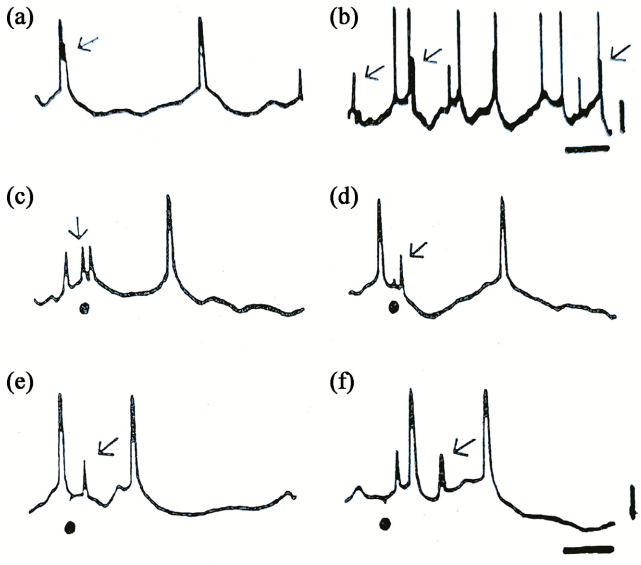

Figure 5. Intracellular recording of TRN neuron activity in response on stimulation (30 μA, 0.5 ms) of the ventro-postero-lateral nucleus ((c), (d)) and the neocortex ((e), (f)). ((a), (b)) spontaneous activity of the neuron. Arrows indicate the moments of origin of dendritic potentials. Calibration: a, c, d, e, f, 4 ms, 20 mV., b, 80 ms, 20 mV.

have a constant amplitude and a temporal flow. The figure shows, that both potentials have a constant amplitude and a temporal flow. It should be especially noted that the generation of one action potential does not prevent the generation of another, *i.e.* do not cause mutual refractoriness. The figure shows that the peak potential of smaller amplitude can occur on the ascending or descending phase of the spike potential of large amplitude ((a), (b)). The most probable assumption from these facts, and also taking into account that the probability of introducing the microelectrode into the soma is greater than in the dendrites, is that the peak potential of a smaller amplitude is generated somewhere on the dendrites. The spike potential of large amplitude, apparently, is somatic.

In response to stimulation of the specific nucleus of the thalamus, after a potential of smaller amplitude, hyperpolarization and a spike potential of large amplitude occur ((c), (d)), and when the neocortex is stimulated, both spikes are repeated several times ((e), (f)).

Without going into the results in detail, we can conclude that in this case the afferent fibers of both specific nucleus of the thalamus and neocortex act on the dendrites of NRT neurons and cause the development of spreading action potentials. This is not surprising, since all axons connecting thalamic nuclei and cortical areas in both directions send collaterals to TRN neurons [2] [4].

It is well known that in order to implement integration in the Sherrington sense [13], the perceiving part of the neuron, dendrites, must sum up gradual excitatory and inhibitory actions. In other words, our general understanding of the function of neurons is that dendrites receive information that is relayed to the axon, where action potentials are initiated and propagated to eventually trigger neurotransmitter release at synaptic terminals. Although for a number of neuron types in the mammalian brain, many neuron types do not follow this classical polarity pattern. In fact, dendrites may be the site of action potentials initiation and propagation. It has been shown that chromatolized spinal motor neurons can generate dendrite peak potentials [14]. In these motor neurons, each dendrite can generate an action potential that is conducted to the soma, and the soma itself is the point of summation of peaks coming from different dendrite segments. In the aftermath, dendrite peak potentials have been described during intracellular recording of the activity of hippocampal neurons [15]. Despite this, the question remained open: are the lower amplitude potentials really dendritic peaks, or are they local responses of a decremental nature. The final answer to the question was obtained by intradendritic recording of the activity of Purkinje neurons of the cerebellum [16]. So the dendrites of some neurons of the central nervous system are capable of generating peak potentials. However, it should be noted that convincing evidence for the existence of dendrite action potentials has recently been obtained for hippocampal and neocortical neurons [17] [18] [19] [20] [21]. As for the dendrite potentials of thalamic neurons in general and the reticular nucleus of the thalamus in particular, it has not yet been studied reported.

Our data do not give us the right to state with certainty that the peak potentials of smaller amplitude that arise in TRN neurons are of dendritic origin, but at the same time, according to some criteria, they are similar to dendritic propagating potentials that were described in other works. Namely, as noted above, activity was recorded intra-somatically, peak potentials of smaller amplitude arose according to the all-or-nothing law, they are always of the same amplitude and duration, the generation of one potential of large amplitude does not prevent the emergence of another potential of smaller amplitude, in other words, they do not cause mutual refractoriness.

It should be immediately noted that the recorded TRN neurons are not damaged, because the recording of neuronal activity was carried out for more than 35 min. It has been proven that damaged neurons can be recorded for no more than 10 - 15 minutes [22].

4. Conclusion

From all that have been said, the ability of TRN neurons to generate dendrite propagating impulses can be considered quite justified. Both the strategic position and the functional purpose of the TRN give the right to such an assumption. Therefore, TRN neurons must each time be discharged by propagating spike potentials in order to exert their modulating effect without leakage. If we succeed in further carrying out intra-dendritic recording of TRN neurons, then we can talk about the intimate mechanisms of the generation and conduction of these action potentials.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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