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Theta Rhythm Enhancement and Seizure Suppression by Ventral Tegmental Area Stimulation in Epileptic Rats

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Abstract

At present, a number of epileptic attack forms are intractable (not sensitive to pharmacological treatment). Deep brain stimulation (DBS) is used as an alternative therapeutic procedure for pharmacoresistant psychiatric disorders. The results of using such methods have, however, contradictory. This is why structures whose stimulation is capable of inducing an antiseizure effect by preventing initiation and/or spread of epileptiform reactions have not yet been adequately identified. The aim of our study was to investigate the effects of short-term and long-term ventral tegmentum area (VTA) stimulation on local and generalized hippocampal seizure responses. Hippocampal seizure reactions were considered local if convulsive discharges were not registered in the electrical activity of the neocortex and behavioral seizures did not developed. It was shown that long-term (30 sec) stimulation of the VTA significantly reduced the development of local hippocampal seizure responses. It was also shown that with long-term (8-10 min) stimulation of the VTA, there is a strong and long-term inhibition of the convulsive reactions of the hippocampus. The present study shows that the ventral tegmental dopaminergic system, which is involved in the regulation of hippocampal theta rhythm and emotional responses, may trigger the activation of mechanisms that are characterized by anticonvulsant activity. The strong inhibitory effect of VTA stimulation on the hippocampal seizure responses is due to 1) regulation of the hippocampal theta rhythm, 2) potentiation of dopaminergic synapses, and 3) involvement of the reticular nucleus of the thalamus.

Keywords

Deep Brain Stimulation (DBS), Ventral Tegmental Area (VTA), Epilepsy, Pharmacoresistant Epilepsy, Hippocampal Seizure.

INTRODUCTION

At present, a number of forms of epileptic attacks are intractable (not sensitive to pharmacological treatment). Emotional disturbances are often experienced by patients with temporal lobe epilepsy. These emotional disturbances may occur interictally (i.e. between seizures) and may profoundly change the individual`s personality. The researchers' primary focus is on the influence of animal (kindling model) and human epilepsy on emotional behavior, rather than vice versa. We are interested in establishing the influence of emotional reactions on epileptic activity, in other words, are interictal emotional disorders protective for the epileptic brain or a risk factor?

Previously it has been demonstrated that during simultaneous stimulation of the hippocampus and the structure whose activation causes reactions fear, anxiety and run (dorsomedial nucleus of the hypothalamus – DMH) there is a sharp halt in the development of epileptogenesis in the hippocampus. Also, in the presence of already developed epileptogenic focus, combined stimulation of these structures resulted in suppression of the electrographic and behavioral seizures [1].

At the same time, we also showed that at threshold stimulation of the hypothalamus and/or mesencephalic reticular formation when electrohippocampogram shows augmentation of the theta rhythm there is a significant reduction in seizure durations [2]. In our earlier studies, we examined changes in brain seizure activity caused by stimulation of the hippocampus at different stages of sleep and wakefulness. It was shown that during wakefulness and paradoxical phase of sleep, when theta rhythm arises in the hippocampus, stimulation the hippocampus to be less effective; seizure discharges either are weakened or do not emerge at all [3]. Recently, there has been increased interest in the relationship between the theta rhythm and seizure activity in the brain [4-6].

Since some forms of epileptic seizures are resistant to pharmacological treatment, deep brain electrical stimulation is effective for the treatment of various neurological and psychiatric disorders. Stimulation of many deep brain structures has been tested as a potential means of blocking seizure attacks in humans and experimentally evoked epileptiform discharges in animals. Deep brain stimulation of the globus pallidus,

subthalamic nucleus and thalamus is used to treat symptoms of movement disorders such as Parkinson's disease, dystonia and tremor [7,8]. The mechanisms behind seizure suppression by deep brain stimulation (DBS) are not fully understood, and the most optimal stimulus regimens and anatomical targets are yet to be determined. However, the results of using such methods have been contradictory [9]. This is why structures whose stimulation is capable of inducing an antiseizure effect by preventing initiation and/or spread of epileptiform reactions have still not been adequately identified.

The present study was conducted to determine the influence of the ventral tegmental area (VTA) on local hippocampal and generalized seizure reactions. Experiments will be conducted in Wistar albino rats in which, using conventional methods the state similar to human temporal lobe epilepsy would be artificially elicited (kindling model). In the given paradigms the impact of ventral tegmental area (VTA) on the development/course of seizure activity will be checked, which, in our opinion, is especially important for the scientific analysis of this type of research.

Why ventral tegmental area?
1.The main goal of our research is to establish the relationship between emotions and epilepsy. VTA is involved in various emotional reactions [10-12] 2. VTA is connected to the hippocampus [13] and is involved in the generation of the theta rhythm [14,15]. 3.The hippocampal theta rhythm is a physiological state of the hippocampus, which opposes its recruitment into seizures [16]. 4. Dopamine has an anticonvulsant effect [17-19].

We reported here the results of the following experiments: 1. The influence of the short-term and long-term VTA stimulation on local electrographic convulsive reactions of the hippocampus. 2.The influence of the long-term VTA activation on the generalized seizure reactions induced by stimulation of the hippocampus.

However, there are several studies in the literature demonstrating the effect of VTA on generalized seizures induced after intraperitoneal administration of pentylenetetrazole [9,20].

It was shown that VTA stimulation significantly decreased the pentylenetetrazole-induced epileptiform discharge duration and the seizure behavioral parameters such as maximum seizure stage, stage 5 duration, seizure duration. In addition, focal to generalized seizure latency increased following VTA tonic stimulation. These data suggest that stimulation of VTA before PTZ injection on 4 test days had anticonvulsant effects on PTZ-kindled seizures.

METHODS

Wistar albino and the genetically epilepsy-prone rats weighing 250 to 300 g were kept under conditions of a 12/12 h illumination cycle with free access to food and water. Housing, surgical manipulations 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 (20.11.2019). 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 US Department of Health and Human Services (1986) Guide for the Care and Use of Laboratory Animals [21].

The animals were anesthetized by sodium pentobarbital (40 mg/kg, i.p.). Bipolar stimulating/recording electrodes (stainless steel) were stereotaxically implanted in the ventral hippocampus and VTA [22].

A monopolar recording electrode was placed on the surface of the motor cortex; the reference electrode was fixed between the skull and head muscles. The above-mentioned structures were stimulated at least 12 - 14 days after surgical intervention. After the end of the experiment, the animals were deeply anesthetized. Sites of localization of the tips of the hippocampal and VTA electrodes were coagulated (constant current 2 to 3 mA 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.

Experiment 1

In the first series (n = 8) of these experiments, after implantation of the electrodes into the above-mentioned structures in rats and after the lapse of post-operative period (10 - 12 days) we studied the influence of the VTA stimulation (30 sec-long-series of rectangular 100-120 μA, 0,5 msec-long current pulses) on the course of hippocampal threshold stimulation induced local (without behavioral manifestations) seizure reactions.

In the second series of experiments (n=6), the effect of relatively long-term (8-10 minutes) VTA activation on the local seizure reactions evoked by hippocampal threshold stimulation was studied.

Experiment 2

In these experiments the hippocampus was stimulated using a fast kindling protocol. Ten to 12 days after surgery, the hippocampus was stimulated for one day by 40 stimulation series applied with 5-min-long intervals (duration of sessions 10 sec, intensity 450 μA, frequency 10 sec–1, and stimulus duration 1ms). For estimation of the excitability of the hippocampus and of the stability of manifestations of the epileptic syndrom the 2-nd day and also 2 and 4 weeks after such stimulation, test stimulations were applied to the hippocampus (5 stimulations with 5-min-long intervals). Due to kindling, an epileptogenic nidus was formed in the brain of the animals, and this nidus was preserved for the entire future life period even with no additional stimulation of the hippocampus.

The intensity of seizure activity was estimated according to the modified Racine scale (1972): 0 - immobilization, "freezing in place" of the animal, and shakings; 1 point - jerking of the muzzle; 2 - chewing and shaking of the head; 3 points - clonus of the forelimbs; 4 points - rising in a vertical position and clonic jerks of the forelimbs, and 5 points - vertical position and falling of the animal on its side or back [24].

VTA was stimulated with current pulses of 100-120 μA, with a duration of 0.5 msec and a frequency of 50-80 s, for 8-10 min. The influence of such VTA stimulation on the generalized seizure reactions induced by stimulation of the hippocampus was investigated.

DATA ANALYSIS

Differences between the parameters of kindling-induced behavior were estimated using un-paired *t*-test or factorial dispersion analysis (ANOVA) with a post-hoc Bonferroni–Dunn test. The development of kindling manifestations was estimated using ANOVA for repeated measurements. Intergroup differences were considered to be significant at $P < 0.05$.

RESULTS

The influence of short-term preliminary stimulation of VTA on local convulsive reactions of the hippocampus was studied. Seizure reactions were considered local if convulsive discharges were not

registered on the electrical activity of the neocortex and behavioral seizures did not developed. It was shown that stimulation of the tegmentum significantly reduced the development of local hippocampal seizure responses (Figure 1). Seizure reaction was evoked by stimulation of the contralateral symmetric hippocampal area.

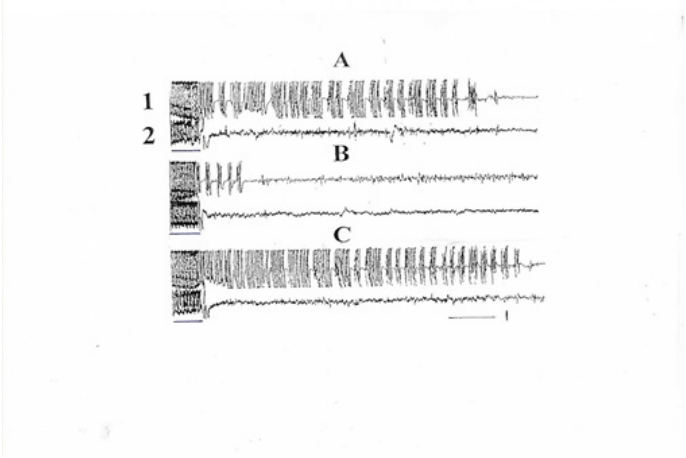

Figure 1: Influence of VTA stimulation on hippocampal-evoked seizure responses. 1 – electrohippocampogram. 2 – Electrical activity of motor cortex. A – Effect of the threshold stimulation of contralateral hippocampus before the stimulation of VTA. B - Effects of contralateral hippocampal stimulation after 2 min activation of VTA (120 μA, 30 sec, 80 Hz). C - Effect of contralateral hippocampal stimulation 15 min after VTA stimulation. Lines under the curves are moments of hippocampal stimulation. Calibration: 2 seconds, 250μV.

It was also shown that with long-term stimulation of the VTA, there is a strong and long-lasting inhibition of the convulsive reactions of the hippocampus. The following figure shows the development/course of hippocampal convulsive reactions caused by stimulation of the contralateral symmetric hippocampal area after 8 minutes of VTA stimulation (Figure 2).

The following figure shows the mean duration of hippocampal electrographic convulsive reactions before and after 10 minutes of VTA stimulation.

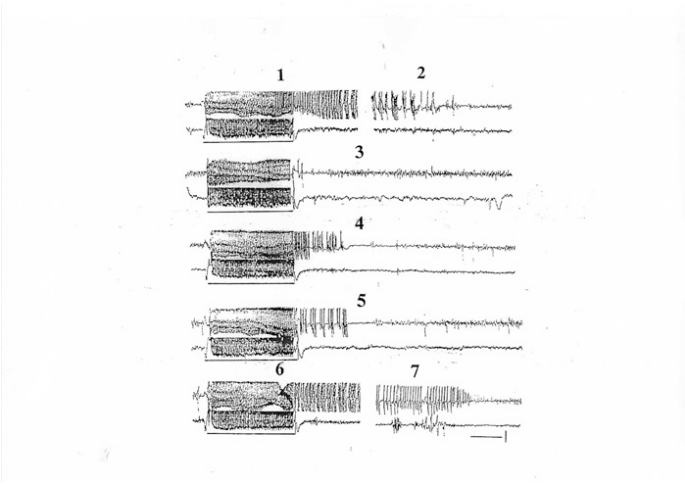

Figure 2: Effect of 10-min VTA stimulation on hippocampal seizure responses evoked by stimulation of the contralateral symmetric hippocampal area. Upper cover– electrical activity of hippocampus, lower cover – electrical activity of neocortex. *1,2 - the effect of threshold hippocampal stimulation. 3 - the effect of hippocampal stimulation 5 minutes after VTA activation. 4 - the effect of hippocampal stimulation 15 minutes after VTA activation. 5 - the effect of hippocampal stimulation 30 minutes after VTA activation. 6,7 - the effect of hippocampal stimulation 45 minutes after VTA activation. Lines under the curves are moments of hippocampal stimulation. Calibration: 2 seconds, 250μV.*

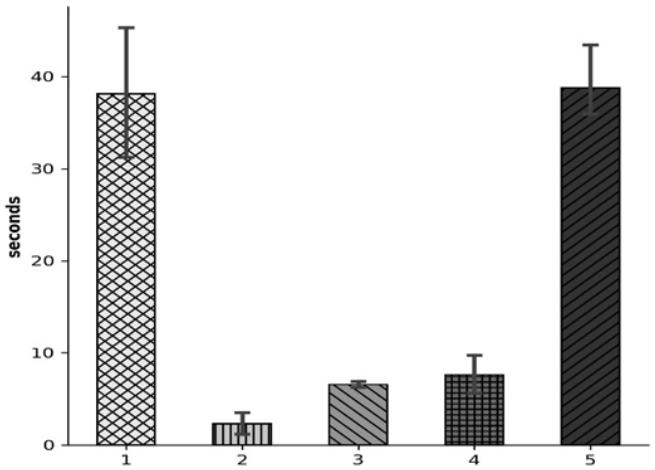

Figure 3: Effect of 10-minute VTA activation on convulsive reactions evoked by hippocampal stimulation. 1 – mean duration of hippocampal convulsions before VTA stimulation. 2 – mean duration of hippocampal convulsions 5 min. after cessation of VTA stimulation. 3 – mean duration of hippocampal convulsions 15 minutes after cessation of VTA stimulation. 4 – mean duration of hippocampal convulsions 30 minutes after cessation of VTA stimulation. 5 – mean duration of hippocampal convulsions 45 minutes after cessation of VTA stimulation.

The data show that VTA stimulation in already established kindling decreases the mean duration of hippocampal afterdischarges (Figure 4), and the mean grade of the behavioral seizures (Figure 5).

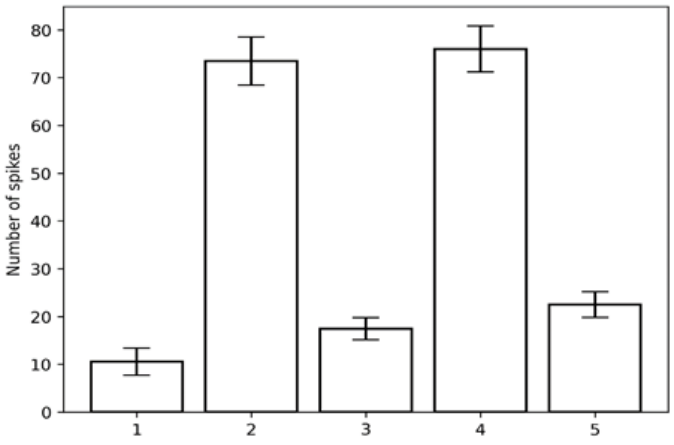

Figure 4: Mean duration of hippocampal afterdischarges in response to isolated hippocampal and combined (VTA - 10 h + hippocampus) test-stimulation at the different time points (2 and 4 weeks). 1 – Effects of the first 5 hippocampal stimulations during the kindling procedure. 2 - Effects of test stimulation of the hippocampus after two weeks. 3 - Effects of test stimulation of the hippocampus after 6-minute stimulation of the ventral tegmentum (2 weeks). 4 - Effects of test stimulation of the hippocampus after four weeks. 5 - Effects of

test stimulation of the hippocampus after 6-minute stimulation of the VTA (4 weeks)

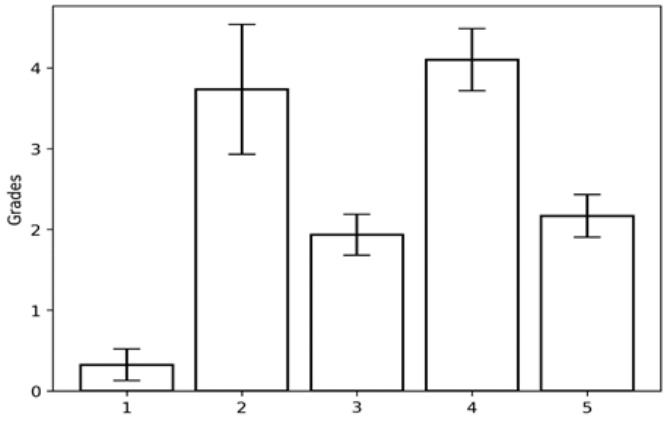

Figure 5: Mean grade of motor seizures in response to isolated hippocampal and combined (VTA - 10 h + hippocampus) test-stimulation at the different time points (2 and 4 weeks). 1 - Effects of the first 5 hippocampal stimulations during the kindling procedure.2 - Effects of test stimulation of the hippocampus after two weeks. 3 - Effects of test stimulation of the hippocampus after 6-minute stimulation of the ventral tegmentum (2 weeks). 4 - Effects of test stimulation of the hippocampus after four weeks. 5 - Effects of test stimulation of the hippocampus after 6-minute stimulation of the VTA (4 weeks)

DISCUSSION

A study of the effect of VTA on local as well as generalized convulsive reactions induced by hippocampal stimulation showed that the preliminary short- and long-time stimulation of VTA caused a blockade of the evoked convulsive reactions of the brain.

However, there are several studies in the literature demonstrating the effect of VTA on generalized seizures induced after intraperitoneal administration of pentylenetetrazole [20].

It was shown that VTA stimulation significantly decreased the pentylenetetrazole-induced epileptiform discharge duration and the seizure behavioral parameters such as maximum seizure stage, stage 5 duration, and overall seizure duration. In addition, focal to generalized seizure latency increased following VTA tonic stimulation. These data suggest that stimulation of VTA before PTZ injection on 4 test days had anticonvulsant effects on PTZ-kindled seizures.

A modulatory effect of low-frequency stimulation in the ventral tegmental area (VTA) on neuronal activity in descending and ascending brain regions was demonstrated in chemically excited mice by assessing c-Fos immunoreactivity. Stimulation in the VTA significantly decreased the c-Fos expressing cells numbers in several brain areas including the hippocampus. These data suggest that the possible anticonvulsant mechanism of DBS in VTA can be through restoring the seizure-induced cellular hyperactivity to normal [9].

In our recent experiments [2] where the effect of stimulation of the hypothalamic and/or mesencephalic reticular formation on the development of kindling was studied, it was shown that stimulation of these structures significantly suppressed the course of both EEG and behavioral seizure reactions. It has been proposed that increased inhibition during hippocampal theta activity may trigger mechanisms that prevent epileptiform activity and that hippocampal theta rhythm is a physiological state of the hippocampus that counteracts its involvement in seizures.

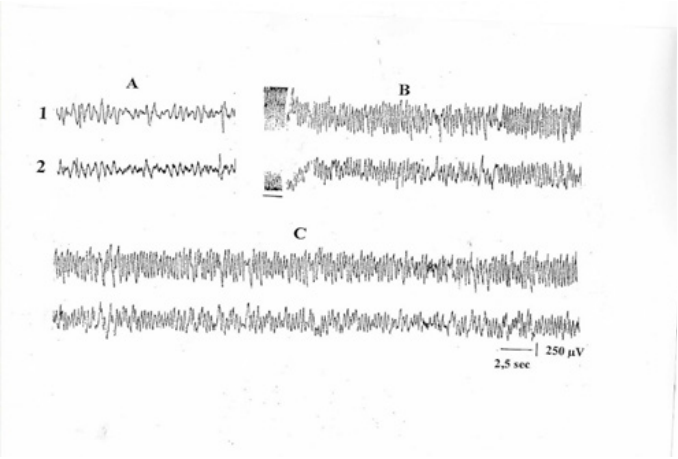

Figure 6: The effect of VTA stimulation on the electrical activity of contra- and ipsilateral areas of the hippocampus. A – background activity of symmetrical areas of the hippocampus. C, D - effects of stimulation (100 мка, 80 Hz, 20 sec) of the VTA. The line indicates the end of VTA stimulation

It turned out that rhythmic slow activity of the hippocampus (theta) is regulated by many structures of the brainstem, including the ventral tegmental area of the midbrain, and that the ventral tegmental area is thought to be an important component in the mesocorticolimbic system involved in the regulation of theta rhythm in the hippocampus [25].

Thus, it was shown that administration of 1.25 μg flupentixol into the VTA induced a prolonged theta rhythm lasting an average of 32.0 min, while 5 μg amphetamine induced a theta rhythm lasting an average of 24.4 min [26]. In addition temporary VTA inactivation resulted in transient loss of the hippocampal theta. Permanent destruction of the VTA caused a long-lasting depression of theta power. Activation of glutamate receptors or decrease in GABAergic tonus in the VTA led to enhancement of dopamine release and increased hippocampal theta power [27].

Based on the above, the results of our experiments, where it was shown that high-frequency stimulation of the VTA caused the emergence of a well-defined theta rhythm in the hippocampus, are not satisfactory.

In the epileptic brain, the frequency of both the hippocampal theta rhythm and septal neuronal theta bursts increased. In the septum, an augmentation of neuronal rhythmicity was also observed. Theta oscillations, either spontaneous or evoked by sensory stimulation, abolished the epileptiform events.

These findings were further supported by [28], which confirmed increased theta frequency in both the hippocampus and septum, along with suppression of epileptiform activity during theta oscillations.

Of particular note is that VTA stimulation caused inhibition of evoked population spikes recorded in the CAI pyramidal cell layer of the hippocampus [29].

The VTA, which may be one of the structures involved in the regulation of hippocampal theta rhythm, sends direct projections to the hippocampus and also to the forebrain septum. Our data suggest that the projection through which the VTA enhances theta rhythm is not direct but is incorporated into the main route of theta generation, which involves the septum as the main relay node [15].

Several studies point to a possible abnormality in the firing pattern of dopaminergic neurons after epilepsy. In particular, there is an increase levels of dopamine. It was also shown that VTA dopamine neurons are reported to be activated and produce more dopamine during epilepsy [5] and elevated dopamine levels and increased firing of dopaminergic neurons have been found in rodent models of temporal lobe epilepsy.

It is especially important to note the data of some authors where the reactions of VTA neurons were studied during convulsive activity in the limbic structures of the brain. Given the evidence that the hippocampus plays an important role in the maintenance of temporal lobe seizures, we investigated whether an animal model of high-grade epilepsy using intrahippocampal injection of pilocarpine induced changes in the activity of mesolimbic dopamine (DA) neurons. It was shown, that 60% of rats in which pilocarpine induced seizure activity had a significant increase in the number of DA neurons [30]. It has also been shown that dopamine neuron degeneration in the Ventral Tegmental Area causes hippocampal hyperexcitability [6].

Taking into account the data from our early studies, as well as the results of the present experiments, the question arises about possible mechanisms of suppression of hippocampal local and generalized convulsive reactions of the brain.

Some authors mentioned that activation of the septo-hippocampal pathways resulting from sensory stimulation or stimulation of the hypothalamus and a few brainstem structures is accompanied by a decrease in the frequency of spiking of hippocampal pyramidal neurons. On the other hand, it was shown that the frequency of discharges of hippocampal interneurons increased in this case. Basket cells represent the most numerous morphological type of hippocampal interneurons; from the functional state, they are believed to be inhibitory units [31-33]. Precisely hippocampal interneurons are generally classified as theta cells. Therefore, reciprocal relations between the intensities of seizure and theta activity can be interpreted as a sort of regulatory effects provided by inhibitory mechanisms under conditions of generation of the theta rhythm. Our findings allow us to suppose that augmentation of inhibitory processes (activation of the interneurons) in hippocampal neurons in the course of VTA stimulation can trigger mechanisms preventing the development of epileptiform activity. We assume that the above is one of the mechanisms for blocking hippocampal convulsive reactions during VTA stimulation.

Our experiments showed that prolonged stimulation of the VTA results in strong and prolonged inhibition of hippocampal seizure reactions. Long-term inhibition of hippocampal seizure reactions in this case can also be explained by long-term potentiation of dopaminergic neurons induced by VTA stimulation.

Functional connections between the VTA-DA and the reticular nucleus of the thalamus suggest the involvement of this thalamic nucleus in blocking generalized convulsive reactions caused by stimulation of the hippocampus [34]. GABAergic TRN neurons have one of the highest densities of D4-type dopamine receptors in subcortical structures [34]. It was shown, that the activation of dopamine D4 receptors modulates GABA release in slices of the rat thalamic reticular nucleus. Given the importance of the TRN in the control of attention and sensory processing it is possible that abnormal TRN function may generate some of the manifestations of the disorders of dopaminergic transmission [35].

Studies by Mitchell J, et al. [35*] confirmed the expression of D1 and D4 and showed that D2 receptors are also expressed in TRN.

Barrientos R, et al. [34] showed, by recording single neurons of the TRN, that: 1) there is a tonic dopaminergic input to the TRN; 2) local activation of D4 receptors increases the basal firing rate of TRN neurons.

Although the exact mechanisms of action of DBS are still elusive in despite of extensive research, several theories have been put forward. These proposed mechanisms can be divided into acute (seconds to hours) and chronic (days to months). Electrophysiological and neurotransmitter modulation likely explain the acute effects whereas plasticity and neurogenesis may explain the chronic effects [36].

In this respect, the following fact is rather interesting. Direct stimulation of the TRN can significantly suppress generalization of motor limbic seizures within the dynamic phase (epileptogenesis) and decrease manifestations of seizure activity related to pre-formed limbic epilepsy [37].

CONCLUSION

The present study shows that the ventral tegmental dopaminergic system, which is involved in the regulation of hippocampal theta rhythm and emotional responses, may trigger mechanisms by anticonvulsant activity. The strong inhibitory effect of VTA stimulation on the hippocampal seizure responses is due to 1) regulation of the hippocampal theta rhythm, 2) potentiation of dopaminergic synapses, and 3) involvement of the reticular nucleus of the thalamus.

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