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Paleocerebellar electrical stimulation induces the reduction of seizures and the development of absence epilepsy in rats with penicillin-induced epilepsy

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ABSTRACT

Administration of benzyl penicillin (300,00000 IU/kg, i.p.) in free moving Wistar rats causes the precipitation of spikes and generalized ictal potentials with a life-span of epileptic activity up to 6 hours. Periodic electrical stimulation (ES) of the paleocerebellum (100 Hz, 1 ms, 100-180 μA duration of trial 1 s, inter-stimulus interval 3.5-4.0 min) is followed by a significant decrease of the power of epileptic activity, starting at the end of the second hour of stimulation. Moreover, a reduction of the duration of epileptic activity up to 4.0 hours was seen. In the frontal cortex spike-wave discharges (4-5/sec) can be registered starting from 135 to 175 minutes after stimulation. Spike-wave precipitation is followed by a decrease of the amplitude of spikes, by epileptic clonic seizures, by the development of freezing behavior, by tremor, chewing and licking and by other minor signs of absence epilepsy, by vibrissae twitching, by accelerated breathing, head tilting and by eye twitching. Hence, evidence on the absence form of epilepsy precipitation in the course of paleocerebellar-ES-induced suppression of generalized penicillin epilepsy is gained.
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1. Introduction

Cerebellar aspiration as well as the damage to the cerebellar cortex and nuclei is followed by the increase of brain excitability along with an intensification of epileptogenic phenomena (Gartside, 1978; Kryzhanovsky, 1986; Godlevsky et al., 2002). Electrical stimulation (ES) of cerebellar structures is followed by either intensification or a suppression of epileptic manifestations. The outcome depends on the characteristics of the epilepsy model, the functional state of the stimulated structure, and the parameters and regimens of ES (Hablitz and Rea, 1976; Lockard et al., 1979; Laxer et al., 1980; Shandra et al., 1994; Godlevsky et al., 2002; Godlevsky et al., 2004; Rubio et al., 2004; Shandra and Godlevsky, 2005). The synaptic output organization of the irritated cerebellar zone is also contributive: ES of paleocerebellum is followed by the activation of the brain stem nuclei (Bantli and Bloedel, 1975; Laxer et al., 1980) which are able to suppress epileptic phenomena (Shouse et al., 1989). That is why paleocerebellar structures are relatively more potent with regard to the origin of antiepileptic effects in comparison with the other cerebellar structures. Thus, neocerebellum affects cortical epileptogenesis via thalamic nuclei, and a low-frequency of the neocerebellar ES might be provocative for both thalamocortical synchronization and epileptic activity generation (Kryzhanovsky, 1986; Godlevsky et al., 2002).

Effects of cerebellar ES are more pronounced in generalized seizure forms of epilepsy. In fact such forms, especially when in case of drug-resistance, serve most frequently as targets for a clinical implementation of cerebellar-ES treatment of epilepsy (Majkowska-Zwolinska and Zurawska, 1998; Davis, 2000; Velasco et al., 2005; Brighina et al., 2006; Morrell, 2006; Lockman and Fisher, 2009; Kahane and Depaulis, 2010; Lega et al., 2010). Consequences of cerebellar ES on the absence seizures, however, were not in the scope of systematic investigations. It should be noted that Hablitz and Rhea, (1976) described the suppression of penicillin-induced spike-wave discharges (SWDs) in cats, but those influences were promoted by reticular formation activation, which might be regarded as a non-specific mode of affecting the epileptic electrographic equivalent of absence seizures (Coenen et al., 1991; Coenen, 2000; Kostopoulos, 2000; Meeren et al., 2004).

Taking into consideration the fact of suppression of both penicillin-induced seizure foci as well as generalized seizures in the course of cerebellar stimulation, (Godlevsky et al., 2002; Godlevsky et al., 2004) it could be suggested that strengthening of GABA mechanisms are activated by such stimulation in zones of penicillin application. That is why the main assumption, based on the opposite character of the GABAergic inhibition state in generalized and absence forms of epilepsy, (Fromm, 1988; Kostopoulos, 2000) is that cerebellar ES might activate the absence form of epilepsy. As far as penicillin is able to induce wide range of electrographic epileptic manifestations (inter-ictal, ictal and absence-like SWD), in the present work the effects of paleocerebellar ES on penicillin-induced epilepsy was investigated in rats with the emphasis on transition of different types of epileptic activity.

2. Material and methods

Animals

Seventeen male Wistar rats, weighting 230-270 g, were used as experimental subjects. They were kept under standard laboratory conditions. The temperature was kept constant on 23°C, the relative humidity was 60%, the dark/light cycle was 12-12 h, and rats got a standard diet and tap water which was present ad libitum. Procedures involving animals and animal care were conducted according to the university guidelines that comply with international laws and policies [European Community Council Directive 86/609, OJ L 358, I, December 12, 1987; National Institute of Health Guide for Care and Use of Laboratory Animals, US National Research Council, 1996].

General surgery

Registration electrodes (nichrome wires with outer diameter 0.12 mm) were implanted under Nembutal (Pentobarbital®) anaesthesia ("Ceva", France, 40 mg/kg, i.p.). Two recording electrodes were placed in the frontal and two in the occipital regions in both hemispheres (coordinates: AP=1,2; L=3,0; H=1,0; AP=7,8; L=3,0; H=1,0] (Paxinos and Watson, 1998). Stimulation electrodes were nichrome bipolar electrodes (outer diameter 0.12 mm, inter-electrode distance 0.2 mm), which were inserted to the caudal part of the paleocerebellum (uvula, nodulus) under visual control, and have been located on the surface of cerebellum. All electrodes were fixed to the skull with quick-drying dental cement. Starting one week after surgery, rats were handled daily and were adapted to the experimental set-up.

Registration of EEG and the model of epileptic seizures

All observations started not earlier than 10 days after the operation, and the generalized form of seizures was induced via i.p. benzyl penicillin sodium salt administration (300.000 IU/100 g, i.p. in a volume of 0.5 ml of saline) (Marangoz and Bağirici, 2001).

The following EEG registrations (bipolar) were made: lead #1- frontal-occipital zones of the left hemisphere; lead #2- frontal-occipital zones of the right hemisphere; lead #3- frontal zones of both hemispheres and lead #4- occipital zones of both hemispheres. The analogue data were digitized with a sample frequency of 256 Hz, while the time constant that was used was 0.1 and the low-pass filter was set at 70 Hz. Inter-ictal discharge frequency estimation was made during each 1-min period of registrations during all observations.

Stimulation of the cerebellum

ES of the cerebellum was started at 20-40 μA (60 Hz, duration 1 ms, duration of trial 1 s), and every 4.0 min, 20 μA was added until the behavior reaction was induced (turning, freezing of rats). Afterward, the intensity of ES was reduced by 30%. ES of the cerebellum was performed with the inter-stimulus interval of 3.5-6.0 min. The intensity of electric current used for cerebellar ES was 100-180 μA and duration was 2.0-3.0 s. ES started in 5.0-7.5 min from the moment of appearance of spontaneous seizure discharges. Total number of stimulative seria was from 27 to 70 per rat. The intensity of ES did not disrupt the locomotors activity of freely moving rats and did not modify their behavior as well. Control group of animals (9 rats) were connected with the wires, but ES was not performed. The life-span of epileptic activity was determined in a period from the first till the last spike (Gartside, 1978).

Histology

At the end of the experiments, the rats were anesthetized with pentobarbital sodium and perfused with paraformaldehyde. Frozen sections (32 μm) of the whole brain including cerebellum were prepared and every alternate section was mounted on gelatine-coated slides, stained with neutral red, covered with a cover-slip, and examined by the light microscopy. Only those rats with appropriate location of electrodes were used in the final analysis of the data.

Data analysis

The index of the frequency of discharges and the life-span of epileptic activity was analyzed by a one-way ANOVA, followed by the Newman-Keuls test. Data were presented as M± S.E.M. The number of animals with ictal discharges in two groups (experimental and control) was estimated by z-test for two proportions. Estimation of the relationship between ES and incidence of SWD generation was performed on the next basis. In each rat starting from the moment of appearance of SWD (135.0-175.0 min from the moment of first ES) next 10 stimulative trials have been analyzed. Period between two consequent ES was subdivided on first and second equal part, and those ES which have been accompanied by the appearance of SWD during first half of poststimulative period have been regarded as effective one and marked with "+". Correspondently appearance (or absence) of SWD during second part of poststimulative period was in favor for negative result of ES and they have been marked with "-". Hence, totally 80 ES have been taken into consideration and two proportion–positivity per 80 and negativity per 80 trials have been estimated using by z-test for two proportions.

3. Results

Time-course of the penicillin-induced seizures in control rats

To characterize the evolution of benzyl penicillin-induced seizures the registrations of nine rats were used. The first spike discharge was evident in 2.5-9.5 min after the moment of administration of penicillin solution, and in 6 rats out of 9 ones they appeared in the left hemisphere and in 3 rats in the right hemisphere. The occipital cortex was the first EEG lead at which the signs appeared.

The first ictal EEG signs were observed in 16.0-122.0 min

from the moment of administration of penicillin, and during 6 h of observation from 2 up to 20 ictal periods of activity were registered in the control group of rats. The duration of intervals between ictal discharges ranged from 2 up to 23 min.

The maximal frequency of inter-ictal spike discharges (22.5+2.5/min) was seen in 1.5-2.5 h from the moment of appearance of epileptic discharges (Fig.1).

Epileptic activity in the brain structures was present during six hours after the moment of administration (309.8+13.6 min).

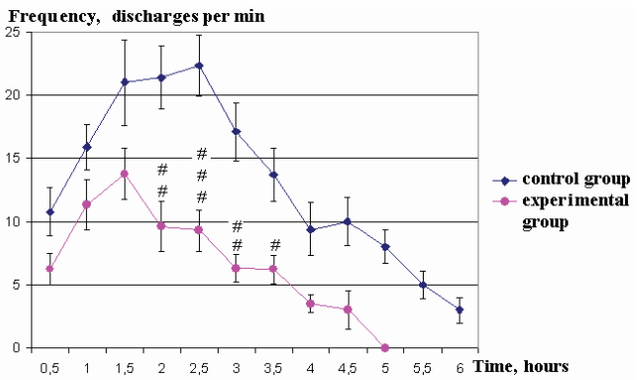

Fig. 1. The influence of paleocerebellar ES upon dynamic of frequency of penicillin- induced discharges (M+ m).
Notes: abscissa- time of observation from the moment of i.p. administration of benzyl penicillin solution (300.000, 00 IU/100 g); ordinate- frequency of interictal spikes generation (per 1 minute). #- P<0.05, ##- P<0.01, and ###- P<0.001 when compared with the corresponded index in control group of rats (ANOVA + Newman-Keuls test).

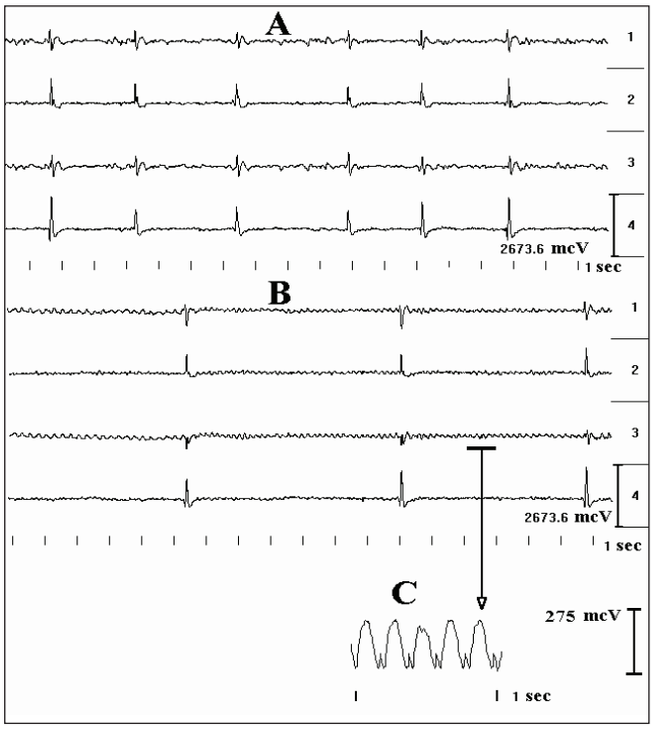

Fig. 2. Precipitation of SWD in the course of paleocerebellar ES in freely moved rats with penicillin- induced generalized form of epilepsy. A-175 min from the moment of benzyl penicillin sodium salt administration (300.000, 0 IU/100 g, i.p., 40 ES were performed). B-50 min after A (additional 13 ES were made). With a solid line and arrow the magnified period of EEG recording is indicated (C).
Lead#1- frontal- occipital zones of left hemisphere.
Lead#2 - frontal- occipital zones of right hemisphere.
Lead#3- frontal zones of both hemispheres.
Lead#4- occipital zones of both hemispheres.
Calibration for fragments "A" and "B": distance between leads (right vertical line, lead N4) is equal to 2673.6 μV. Calibration at "C" is marked with vertical line on the right side (275 μV). Time: 1 sec is marked with regular vertical lines organized in horizontal row at the bottom of fragments.

Cerebellar ES

The measurement of inter-ictal spike frequency revealed that this index was reduced by 51.2% - up to 9.9+1.8/min compared to the corresponding one in the control group of animals in the 2 h from the moment of the beginning of ES (F(1.15)=13.10, P<0.01) (Fig. 2). During the next 0.5 and 1.0 h the difference between groups achieved 58.3% (F (1.15) =19.45, P<0.001), and 63.2% (F (1.14) =15.08, P<0.01) correspondingly (Fig. 2).

The reduction of inter-ictal discharge frequency was also maintained in 3.5 h from the moment of starting of ES (F (1.13) =7.56, P<0.05) (Fig. 2). In the course of ES the ictal discharge appearance was revealed only in 2 out of 8 experimental animas. The comparison with the control group of animals on the basis of two proportions indices showed the significant differences between groups (z= 2.897, P<0.01).

The span life of foci under conditions of cerebellar ES was shortened up to 238.0+19.5 min, when compared with the corresponding index in the experimental group of rats (F(1.15)=9.49, P<0.01). Appearance of SWD in the course of ES- induced suppression of focal epileptogenesis. In 6 rats out of 8 ones the periods with SWDs (4-5/s) between the 135.0-175.0 min from the moment of ES were registered (Fig. 2B). The amplitude of discharges was from 190 to 220 mV (Fig. 2C). Bilateral frontal cortex registration of ECoG revealed the presence of SWDs, while the occipital bilateral leads were silent or not- regular SWDs (4-5/s) with an amplitude, which did not exceed 120 mcV were registered (Fig. 3B, leads 2 and 4 correspondingly).

The precipitation of SWDs coincided with the decreasing of frequency of spikes generation (by 1.5-3.5 times), while the reduction of the amplitude of discharges was more pronounced in the frontal cortex (by 2.0 times).

SWDs were organized in the prolonged periods (from 20.0- 30.0 sec up to 7.5 min). Shorter periods of SWDs (from 1.5 up to 5.0) appeared with the frequency of 0.5-3.5 per minute and these were observed in the remaining 2 rats.

Positive effect of ES for the induction of SWDs was noted in 53 out of 80 trials, while negative one- in remaining 27 out of 80 (z=3.890, P<0.01).

Behavioural ictal ECoG activity was followed by the typical generalized clonic-tonic fits with falling down of rats, and the development of post-seizure depression with the absence of righting reflex was observed. During the period of SWDs no myoclonic seizure reaction was registered, while animals displayed freezing, staring behavior, and subtle tremor of the head. Besides, all rats showed short-term (1.0-3.0) chewing and licking. Other minor behavior disturbances characteristic for the absence type of rat's behavior van Luijtelaar and Coenen, (1986) were also registered: in 7 rats vibrissae twitching were seen along with accelerated breathing (5 rats), head

tilting (4 rats) and eye twitching (1 rat). ES of the paleocerebellum performed during SWDs was not followed by the changes of behavior patterns.

In 4 out of 9 control observation short-term (3.0-5.0 s) periods of freezing, staring have been registered in 95.5- 157.0 min from the moment of epileptogenic administration. In frontal leads SWD bursts with frequency of discharges from 7 to 12/s were detected. Such bursts and behavioural freezing appeared from 3 up to 17 times.

4. Discussion

In freely moving rats it was shown that periodic ES of the paleocerebellar cortex caused a decrease in the frequency of inter-ictal spikes, prevented the incidence of ictal discharges and led to a shortening of the life-span of penicillin-induced epileptic activity in the cortex. The period of declining of the level of epileptogenicity was characterized by the appearance of SWDs with the frequency of 4-5/, which was observed in all cortical zones, while the largest and most pronounced amplitude of the discharges was seen at the frontal leads. The appearance of SWD predisposed the complete suppression of foci activity and was connected with a marked reduction of spike amplitude (especially in frontal leads).

It is also worth to note that the development of SWDs in freely moving rats was accompanied by a specific transition of behavior pattern from clonic manifestations (propagation of spikes) to freezing, staring and tremor, which are quite typical for the absence type of behavior symptoms (van Luijtelaar and Coenen, 1986; Coenen et al., 1992). Hence, these data are in favor for the induction of absence epileptic syndrome in the course of suppression of generalized epileptic activity induced in rats by paleocerebellar ES. In correspondence to the absence-precipitating role of the cerebellum there are data reported by Rubio et al. (2004), who observed the intensification of the initial stage of amygdala kindling in rats by ES of the superior cerebellar peduncle. These data are of interest as far as the beginning of kindling corresponds to the activation of the absence–like mechanisms (Shandra and Godlevsky, 2005).

It should be noted that for SWDs in WAG/Rij rats and GAERS, two commonly accepted rat models for generalized absence epilepsy, Danober et al. (1998) the frequency of 8/sec (in average, for the bandwidth of 7-11) was observed most often (Coenen, 2000). Hence, the rhythm which was registered in the present work, might be regarded as two-time dividing of the frequency of inherited rhythm which is in charge for the absence epilepsy manifestations in the above mentioned rat models. Such a "splitting" of main rhythms is known for rhythmic evoked responses in the cortex and might be explained by modifications in the inhibitory mechanisms in the cortical neuronal chains (Guyton and Hall, 1996). However, 3-5 Hz SWDs was described by Meeren et al. (2004) after chemical lesions of the reticular thalamic nucleus. Finally, Kostopoulos and Gloor, (1982) noticed that after application of penicillin in the feline model the frequency of the slowly decreasing sleep spindles in the process of changing into SWDs also ended up with the frequency half of the frequency of the naturally occurring sleep spindles.

It should also be noted that in our observations more prolonged SWDs were noticed compared to the SWDs registered in typical animal models of absence epilepsy, such as the WAG/Rij rats, in which the mean length of an episode is about 5 (van Luijtelaar and Coenen, 1986; Coenen et al., 1991; Coenen et al., 1992). Described rhythm looks like ictal SWDs seizures which might be maintained by more stable pathogenic synchronization when compared with typical bursts of SWDs in GAERS and WAG/Rij rats (Danober et al., 1998). Hence, the existence of two different mechanisms involved in different types of absence-like seizures manifestation should be suspected. Besides, diminution of spike discharges in the course of generation of SWDs is in favor for antagonistic relationships between these seizure electrographic manifestations. That antagonism was displayed most prominently in frontal cortical zones, which normally are affected by cerebellar transsynaptic efferent influences more specifically than other cortical zones (Guyton and Hall, 1996). Again, reduction of penicillin- induced spikes along with increase of amplitude of SWDs could be explained on the basis of the exertion of hyper-excitable state of GABAergic neurons, which is critical for slow wave precipitation in the SWDs bursts while restoration of GABA-induced neuronal control caused suppression of spikes (Gloor, 1979).

It is worth while to speak of the neurochemical background of the observed effects in the present rat study. It was shown that the GABA receptor agonist muscimol enhanced the number of SWDs, while the antagonist bicuculline reduced the number (Peeters et al., 1989). In line with this is that tiagabine, a GABA-reuptake inhibitor with the strong anticonvulsant properties, enhanced the number of SWD (Coenen et al., 1995). It is in good correspondence with the assumption that activation of SWD might be expected from ES of cerebellar cortical structures as far as the elaboration of GABA is documented (Laxer et al., 1980). Besides, the appearance of agonists of the opiate receptors in the CSF of animals with a stimulated cerebellum Shandra et al. (1994) might also be suspected as the mechanism of intensification of SWD-activation, since SWDs were reported under conditions of stimulation of μ,Δ opiate receptors (Lason et al., 1994; Lason et al., 1997).

Meanwhile, activation of the nor epinephrine system of the brain, induced by cerebellar ES, Laxer et al. (1980) might presumably lead to a decrease of mechanisms of SWDs generation, which are suppressed under conditions of activation of catecholaminergic mechanisms (Buzsaki et al., 1990; Biriukova et al., 2000). Hence, this effect is not in correspondence with the cerebellar causative role in absence-epilepsy behavior. Besides, some discrepancies on the contribution of cerebellum to the rhythmic movements observed during spike-wave pattern of activity were described (Kandel and Buzsaki, 1993). These authors described the correlation of the unit activity of neuronal elements of both cortex and nuclei of cerebellum with SWD or a high voltage spindle in rodents, while rhythmic movements (tremor) were absent in half of the observations. As an explanation of this discrepancy, it should be taken into mind that motor effects from the cerebellum are dependent on the state of inhibition of the output of neuronal structures involved in this process. Moreover, the large and the high inhibition of the spinal motor neurons might be in charge of ameliorating the final motor effect of influences from supraspinal structures (Shouse et al., 1989).

It should be also noted that described data showing determining role of paleocerebellum for SWDs rhythm development on model of penicillin-induced seizures are in correspondence with the well known relationships between cerebellar degenerative and functional disturbances and ab-

sence seizures in tittering mice (Ivanov et al., 2004).

Hence, the data obtained here with respect to the absence of SWDs in control group of rats with penicillin-induced generalized seizures are in favor for the evolutionary view that cerebellar influences are necessary for the reconstruction of the neuronal corticothalamic chain, in such a manner that this chain becomes prone to the demonstration of SWDs. Intensification of GABA mechanisms observed during periods between cerebellar ES might be in charge of such an effect.

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