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Effects of Stimulation of the Inferior Colliculi in Krushinskii–Molodkina Rats

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The effects of chemical and electrical stimulation of the central nucleus of the inferior colliculus on the generation and formation of convulsive manifestations and on the organization of sleep were studied in Krushinskii–Molodkina rats with an inherited predisposition to audiogenic convulsions. Microinjection of quinolinic acid (10 μg in 1 μl of distilled water) or electrical stimulation at a frequency of 70 Hz generated paroxysmal manifestations in the form of intense rotatory movement acts, similar to "wild running" of animals in the initial convulsion-free stage of audiogenic seizures. This provides grounds for suggesting that in Krushinskii–Molodkina rats the inferior colliculi are part of the neural network responsible for the generation and execution of the running stage during the formation of convulsive responses to sound stimuli. Application of these stimuli was also followed by a decrease in the total duration of fast-wave sleep during the poststimulus period. Conversely, electrical stimulation of the inferior colliculi at a frequency of 7 Hz on the background of deep slow-wave sleep induced episodes of fast-wave sleep in the rats; after 3–4 sessions of this stimulation producing this effect, there was an almost two-fold increase in the total duration of fast-wave sleep during the post-stimulus period due to an increase in the number but not the duration of these episodes. These results provide evidence that the inferior colliculi in rats may have a modulatory effect on the functioning of the fast-wave sleep triggering system.

Keywords: Krushinskii–Molodkina rats, inferior colliculi, electrical stimulation, quinolinic acid, paroxysmal manifestations, organization of sleep.

The inferior colliculi in rats of the Genetically Epilepsy-prone Rats (GEPR) strain are known to be the site at which epileptiform audiogenic convulsive seizures are initiated [24–28, 35]. The role of the inferior colliculi in the formation of audiogenic paroxysmal reactions has not been studied in Krushinskii–Molodkina rats, which were developed and have been used in physiological studies in Russia [12, 16]. The only data obtained show that convulsive responses to sound stimuli in rats of this strain are followed by decreases in the numbers of cells in the central nucleus of the inferior colliculi [6], while targeted implantation of embryonic striatal or cerebellar tissue into this structure decreased the intensity of audiogenic convulsions [8]. Furthermore, because of the wide use of Krushinskii–Molodkina rats for studies of the actions of anticonvulsant agents [1, 9, 11, 13–15, 18], there is an urgent need for more concrete explanations of the functional role of the inferior colliculi in the mechanisms of the formation and development of epileptiform convulsive manifestations in animals of this strain, as the similarities in audiogenic seizures between Krushinskii–Molodkina and GEPR rats does not suggest identity in the structural-functional mechanisms of their realization. Attention should be focused on the fact that Krushinskii–Molodkina rats are significantly different from GEPR rats in terms of a number of biochemical parameters. Thus, Krushinskii–Molodkina rats have thyroid hyperfunction [7], while GEPR rats are hypothyroid during the neonatal period [32]. Animals of both strains also differ in terms of baseline (outside of audiogenic seizures) levels of various neurotransmitters. Krushinskii–Molodkina rats show increased dopamine and noradrenaline

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contents in the hypothalamus and striatum and serotonin in the temporal cortex, hippocampus, and medulla oblongata, but not in the striatum [5, 11, 14, 15, 18]. GEPR rats are characterized by normal dopamine and decreased noradrenaline and serotonin levels in the telencephalon, thalamus, hypothalamus, midbrain, and pontomedullary area [23, 29, 39]. As electrical stimulation of brain structures is one of the most useful approaches to identifying their functional roles, the main aim of the present study was to investigate the effects of electrical stimulation of the inferior colliculi on the generation and formation of convulsive manifestations in Krushinskii–Molodkina rats. However, as electrical stimulation induces excitation not only of neurons, but also nearby axons, and because inversion of responses to stimulation can sometimes occur [17, 21], some of our experiments used an alternative method for selective activation of inferior colliculus neurons – administration of the glutamate NMDA receptor agonist quinolinic acid into this structure. The actions of this acid on rat brain neurons show almost no difference from those of NMDA [4]. However, as quinolinic acid is an endogenous intermediate metabolite in tryptophan metabolism, it is utilized more rapidly than NMDA and has significantly lower toxicity [36, 38]. Along with studying the effects of electrical and chemical stimulation of the inferior colliculi, there is also interest in studying changes in the organization of sleep in animals after this type of stimulation, which we believe would allow the nature of the possible effects of the inferior colliculi on the functioning of the systems controlling the sleep–waking cycle to be investigated.

Methods

Experiments were performed on 18 Krushinskii–Molodkina rats (male, weighing 200–270 g) with electrodes previously implanted in the right hemisphere of the brain under Nembutal (60 mg/kg) anesthesia at stereotaxic coordinates [33], which were used for recording brain activity. Silver-plated needles (tip diameter 0.2 mm) in polymer insulation were inserted to a depth of 1–1.5 mm into the skull bone over the somatosensory (AP = –1, L = 4), auditory ((AP = –4.8, L = 7), and visual (AP = –5.6, L = 4) areas of the cortex. One deep nichrome wire (diameter 0.1 mm) in Teflon insulation was implanted in the hippocampus. (AP = –3.1, L = 2, H = 3) as the recording electrode.

One group of rats (n = 10) also underwent implantation of two electrodes for electrical stimulation. One of these, a cathode made from nichrome wire (diameter 0.1 mm) in Teflon insulation, was inserted into the central nucleus of the inferior colliculi (AP = –9.0, L = 1.5, H = 4.5) of the right hemisphere; the other was the anode (a silver wire 0.3 mm in diameter) and was fixed to the left (contralateral) nasal sinus. The remaining animals (n = 8) underwent implantation of conducting cannulas (made from steel injection needles with external diameter 0.8 mm) closed with metal mandrels into the central nucleus of the inferior colliculi on the left side of the brain for subsequent microinjection of chemical solutions. All electrodes and cannulas were fixed to the skull with self-setting glue.

After surgery, each rat was placed in a sound- and lightproof chamber in a Plexiglas cage fitted with an electrodynamic probe to record the actogram, with adaptation to the experimental conditions for 5–7 days including daily connection to the lightweight recording cable. Experiments were performed at the end of the preparation period: animals were connected to a Diana computerized electroencephalogram via the recording cable and recording of actograms and electrograms of the brain structures of interest was performed (with continuous visual monitoring of the animal's behavior) in the band 0.5–35 Hz, with simultaneous data storage (the sampling frequency was 185 Hz) in a computer for computerized spectral analysis. On this basis, each experiment involved determination of the initial characteristics of brain activity in the rats in different states of the sleep–waking cycle. The behavioral effects and changes in the patterns and spectral characteristics of the animals' electrograms were then studied after application of electrical stimulation (with an ESL-2 electrical stimulator to the inferior colliculi) consisting of bursts (1.5–4 sec) of square-wave impulses of duration 0.2 msec, frequency 70 or 7 Hz, amplitude 100 μA, in different states of the cycle. On the basis of our previous studies [3], these stimulation parameters were regarded as optimum for eliciting responses.

Studies of the effects of electrical stimulation of the inferior colliculi on the organization of sleep in rats were performed as follows. Control experiments were initially run on each animal, in which continuous polygraph traces were made for 6 h (starting at 09:00, i.e., when rats sleep best); analysis of these in terms of patterns and spectral characteristics were used to divide the animals' behavior into the waking, slow-wave sleep, and fast-wave (paradoxical) phases of sleep, with assessment of the numbers of phases and total durations. These parameters were used to determine the characteristics of the organization of sleep and waking in rats in normal conditions. In subsequent experiments, one group of animals (n = 4) underwent continuous 5-min electrical stimulation of the inferior colliculi 10 min before the start of polygraph recording. Rats of group 2 (n = 6) started experiments at 08:00. During a period of 1 h, animals in the states of waking or slow- or fast-wave sleep underwent 2–4 sessions of transient (1.5–3 sec) electrical stimulation of the inferior colliculi. At the end of these stimulus periods, starting at 09:00, individual 6-h polygraph recordings were made from animals of both groups and these were used to identify the influences of each type of stimulus on changes in the parameters characterizing the organization of sleep and waking in rats, as compared with animals in normal conditions.

Rats with conducting cannulas implanted into the central nucleus of the inferior colliculi for microinjection of chemical solutions also underwent initial control 6-h experiments to assess the characteristics of the organization of

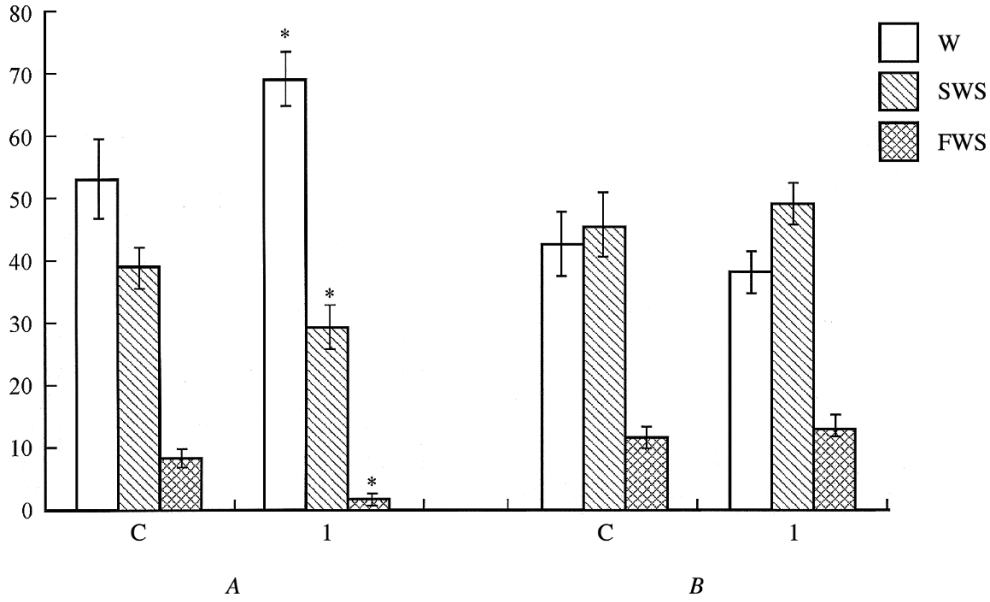

Fig. 1. Organization of sleep in Krushinskii–Molodkina rats in control experiments (C) after administration of 1.0 μl of distilled water into the central nucleus of the inferior colliculi and after injections of 10 μg of quinolinic acid (1) dissolved in 1.0 μl of distilled water into this structure. *A*, *B*) Sequential 3-h intervals after starting control experiments at 09:00 or the recovery period after motor phenomena induced in animals by administration of quinolinic acid. The ordinate shows percentage levels (proportions) of the total durations of waking (W), slow-wave sleep (SWS), and fast wave sleep (FWS), where vertical bars show 95% significance intervals; *significant differences from controls, $p < 0.05$.

sleep and waking in normal conditions. At the beginning of experiments with chemical activation, rats ($n = 4$) previously fixed and in the waking state received 10 μg of quinolinic acid (Fluka, Japan) dissolved in 1.0 μl of distilled water via the conducting cannula with a Hamilton syringe. Control animals ($n = 4$) received 1.0 μl of clean distilled water in analogous conditions. After these operations, fixation was released and a web camera was used to make video recordings of the animals' behavioral reactions, along with 6-h polygraph recordings to identify the nature of the influences of these microinjections on the organization of the rats' sleep and waking. Selection of distilled water for control injections and as the solvent for quinolinic acid was based on studies [10] showing that the use of physiological saline rather than distilled water produced side effects.

After experiments, rats were euthanased under ether anesthesia. Morphological verification of electrode and cannula locations was performed on frontal serial sections of the brain, of thickness 50 μm, using the Nissl method.

Numerical data obtained in the present study were combined for groups of animals and analyzed statistically using Excel 2000. Significant differences were identified using Student's *t* test.

Results

Effects of chemical and electrical stimulation of the inferior colliculi on the generation and formation of convulsive reactions. Microinjection of quinolinic acid into the central nucleus of the inferior colliculi of the rats induced running with turns in the direction contralateral to the hemisphere into which substance was given. The phenomenology of these movements was similar to that of rotatory "wild running" of animals at the initial convulsion-free stage (the running stage) of audiogenic seizures. This type of motor activity continued without break for 15–20 min without any visible convulsive manifestations. The animals then calmed down. In control animals, the response to administration of distilled water into the central nucleus of the inferior colliculi produced no effects.

Application of single electrical stimuli to the inferior colliculi on the background of calm waking, using 1.5–3-sec series of impulses at a frequency of 70 Hz, also evoked circular running with turns in the direction contralateral to the hemisphere in which the stimulating electrode was located. Similar stimulation applied on the background of slow- and fast-wave sleep led to rapid waking of the animals, followed by running in circles. When stimulation was terminated, the animals stopped running 1–3 sec later. If this type of stimulation was applied in the form of a single, long, continuous series of duration 1–10 min, the animals exclusively ran in circles throughout the stimulation period without transferring to the convulsions stage, which was significantly different in phenomenological terms from the pattern of development of pure audiogenic convulsive seizures in these animals, when the running stage was fol-

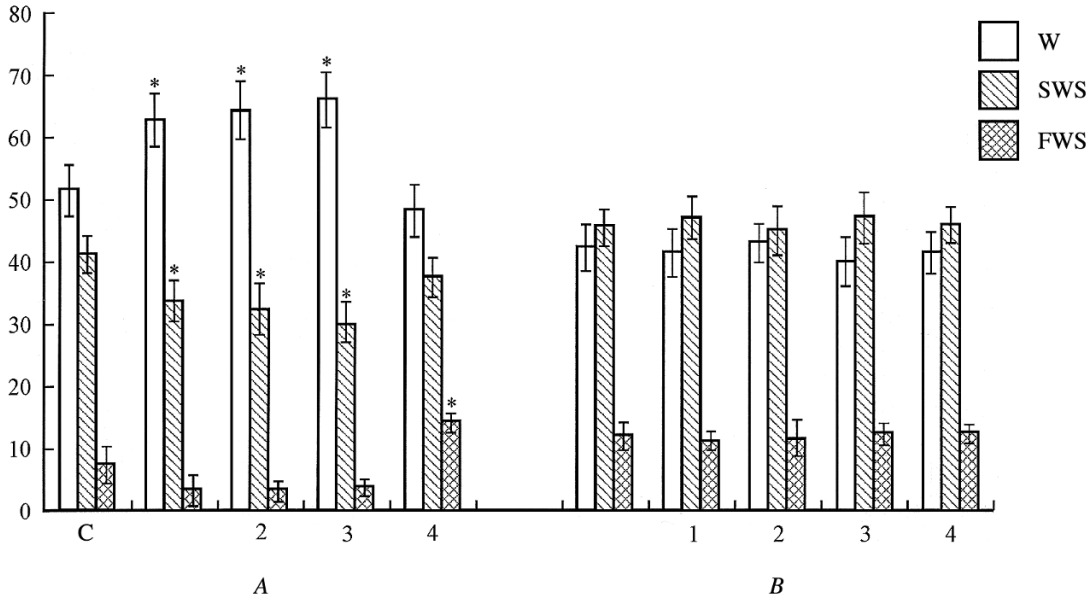

Fig. 2. Organization of sleep in Krushinskii–Molodkina rats in control experiments (C) on connection of animals to the recording cable and placing them in the experimental chamber after sound stimulus-evoked audiogenic paroxysmal seizures in the form of motor arousal without generalized convulsions (1), after single prolonged (5 min) (2) and multiple (four in 1 h) transient (1.5–3 sec) (3) applications of electrical stimuli to the inferior colliculi at a frequency of 70 Hz, and after multiple (2–3 in 1 h) transient (1.5–3 sec) applications of electrical stimuli to this structure at a frequency of 7 Hz on the background of deep slow-wave sleep (4). *A*, *B*) Sequential 3-h intervals after starting control experiments at 09:00 or the recovery period after audiogenic seizures or electrical stimulation. The ordinate shows the percentage extents (proportions) of the total durations of waking (W), slow-wave sleep (SWS), and fast wave sleep (FWS), where vertical bars show 95% significance intervals; *significant differences from controls, $p < 0.05$.

lowed immediately by a seizure generalization stage with the development of clonic and tonic convulsions.

Single applications of electrical stimulation to the inferior colliculi on the background of all phases and stages of the sleep–waking cycle in rats using bursts of 1.5–3 sec at an impulse frequency of 7 Hz were not accompanied by any motor phenomena. These stimuli did not alter the patterns or spectral characteristics of electrograms from the brain structures of interest, did not interrupt sleep phases, and did not induce transitions from one stage of the cycle to another. However, after two to three such applications of electrical stimulation with intervals of 30–60 sec on the background of deep (but not shallow) slow-wave sleep, rats generally showed a transition from slow-wave to fast-wave sleep, with a latent period of 12–49 sec. This type of stimulation on the background of fast-wave sleep did not interrupt this state and had no effect on its duration.

Effects of chemical and electrical stimulation of the inferior colliculi on the organization of sleep. Studies of changes in the organization of sleep in rats after injections of quinolinic acid into the central nucleus of the inferior colliculi showed that clear impairments to the organization of sleep were seen during the first three hours after running induced by administration of this substance ended, these being apparent as a statistically significant increase in the total proportion of waking, compared with controls, with a decrease in the total durations (proportions) of slow- and fast-wave sleep (Fig. 1, *A*). During the next three hours of the recovery period following administration of quinolinic acid, the total proportions of waking, slow-wave sleep, and fast-wave sleep were comparable with those in controls, evidencing recovery of normal sleep organization (Fig. 2, *B*).

Analogous, though less marked changes in the organization of sleep were also seen after prolonged (5 min) continuous or transient (1.5–3 sec) but multiply repeated (four times in 1 h) applications of electrical stimuli to the inferior colliculi with a frequency of 70 Hz (Fig. 2). These stimulus applications, as noted above, evoked circular running in the rats. Disorders of sleep organization seen in animal after these treatments were almost completely identical to the sleep disorders which we previously reported [2] in Krushinskii–Molodkina rats after incomplete audiogenic paroxysmal seizures, consisting of motor arousal without generalized convulsions, limited exclusively to the running stage. Comparison of these results with data from our previous report is shown in Fig. 2.

Given, as noted above, that repeated (2–3 times) applications of electrical stimuli with a frequency of 7 Hz separated by intervals of 30–60 sec, delivered on the background of profound slow-wave sleep led to transition from slow-wave to fast-wave sleep, it was important to study the influences of this type of stimulation on the organization of sleep and wak-

ing in animals. When 3–4 sessions of these stimulation were delivered in one hour on the background of waking or shallow slow-wave or fast-wave sleep, there were no changes in the organization of sleep as compared with controls. If these stimuli were delivered on the background of episodes of deep slow-wave sleep and each session ended with a transition from slow-wave to fast-wave sleep, significant (almost twofold) increases in the duration of fast-wave sleep from the control level were seen during the subsequent 3 h (Fig. 2, *A*) because of an increase in the number but not the duration of these episodes. These results provide evidence that the inferior colliculi in Krushinskii–Molodkina rats may exert a modulatory activating effect on the system triggering fast-wave sleep on the background of slow-wave sleep.

Discussion

The nature of behavioral reactions in Krushinskii–Molodkina rats after chemical (microinjection of quinolinic acid) or electrical (at a frequency of 70 Hz) stimulation of the central nucleus of the inferior colliculi provides evidence of the activatory influences of these stimuli. These influences result in the generation of paroxysmal manifestations as intense rotatory motor acts resembling "wild running" by animals at the initial convulsion-free stage of audiogenic seizures. In addition, the actions of these stimuli are insufficient to generate the complete spectrum of convulsive manifestations or to achieve the maximum extent of seizures with the production of clonic and tonic convulsions. Paroxysmal manifestations of similar type and intensity were seen in Sprague-Dawley and GEPR rats in response to electrical stimulation of the inferior colliculi [24, 31] or administration of glutamate agonists into this structure [24, 27]. We believe that this similarity provides grounds for suggesting that the inferior colliculi in Krushinskii–Molodkina rats, as in rats of these other strains, are involved in the neural network responsible for generating and realizing the running stage on formation of convulsive responses to sound stimuli. In the light of current concepts of the mechanisms of development of audiogenic convulsive seizures in rats with an inherited predisposition to audiogenic convulsions [26], it is completely understandable why chemical or electrical stimulation of the inferior colliculi in these animals does not produce generalized convulsions or the occurrence of clonic or tonic seizures, as occurs on development of convulsive reactions in response to powerful sound stimuli. The essence is that the inferior colliculi of these rats have a deficit of GABAergic inhibition. This is supported by the observation that exposure to powerful acoustic stimuli induces extreme activity of excitatory neurons in this structure, initiating generalization of audiogenic seizures via involvement of the deep layers of the superior colliculi, the periaqueductal gray matter, and the reticular formations of the substantia nigra and pons, while triggering of motor convulsions via the reticulospinal projections. As chemical and electrical stimulation are not selective and elicit activation of both excitatory and inhibitory neurons in the inferior colliculi, the discharge intensity of excitatory neurons in these conditions does not reach a level sufficient to cause generalization of convulsions and induction of seizures. In addition, because of the predominance, due to deficiency of GABAergic inhibition, of the excitatory output from the inferior colliculi to the overlying brain structures mediating convulsive responses activation of these structures nonetheless occurs and convulsive manifestations arise in the form of intense rotatory motor acts.

Attention should also be drawn to the observation that electrical stimulation of the inferior colliculi in Krushinskii–Molodkina rats with series of high-frequency impulses at 70 Hz or microinjections of quinolinic acid into this structure led to decreases in the total duration of fast-wave sleep during the poststimulus period. We have previously reported an analogous decrease in the proportion of fast-wave sleep in rats of this strain [2] after audiogenic seizures of different intensities, and these were due to impairment to the functioning of the mechanisms triggering this sleep phase. In addition, electrical stimulation of the inferior colliculi on the background of deep slow-wave sleep with series of 1.5–3 sec with an impulse frequency of 7 Hz was followed by the occurrence of episodes of fast-wave sleep in the rats. Furthermore, after 3–4 sessions of this type of stimulation ending with this effect, there was an increase in the total duration of fast-wave sleep during the poststimulus period. Similar phenomena consisting of increases in the proportion of fast-wave sleep, linked with activation of the inferior colliculi, have been seen in rats, cats, and humans after repeated sessions of rhythmic auditory stimulation [19, 20]. All these points provide grounds for the conclusion that the inferior colliculi in rats, acting via the relevant projections [22, 28, 34], may have a modulatory effect on the functioning of the centers triggering fast-wave sleep located in the area of the pons [30, 37]. As demonstrated in our studies, the nature of these influences is far from unambiguous. High-intensity arousal of the inferior colliculi (action of quinolinic acid, electrical stimulation at 70 Hz) produces blockade of the system triggering fast-wave sleep, while moderate arousal (electrical stimulation at a frequency of 7 Hz), conversely, activates the operation of these systems. These results are important for understanding the mechanisms regulating the sleep–waking cycle.

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