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Effects of Ionotropic Glutamate Receptor Blockers on Pentylenetetrazole-Induced Seizures in Krushinskii–Molodkina Rats

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Krushinskii–Molodkina (KM) rats have a genetic predisposition to increased audiogenic convulsive readiness and respond to sound signals with clonic-tonic convulsive seizures reminiscent of epileptic attacks in humans. The aims of the present work were to compare the neurological manifestations of the convulsant pentylenetetrazol (corazol) in Wistar and KM rats, i.e., to identify the contribution of genetically caused audiogenic convulsive readiness, and to assess the abilities of the NMDA receptor blockers memantine and 1-phenylcyclohexylamine (IEM-1921) to prevent the actions of pentylenetetrazol in KM rats. Convulsive reactions to administration of pentylenetetrazol were significantly stronger in KM rats than in Wistar rats, and deaths in KM rats were 2.1 times more frequent. Both blockers demonstrated the ability to reduce convulsive reactions to administration of pentylenetetrazol; the prophylactic action of IEM-1921 was more marked. IEM-1921 decreased the mean intensity of convulsive seizures by 2 points on a 5-point scale, while the total duration of generalized seizures decreased 41-fold. IEM-1921 completely prevented deaths among the animals, while memantine produce no more than a tendency to a decrease in lethality (68% in controls, 50% after administration of memantine). The results obtained here provide evidence that NMDA glutamate receptors play an important role in the molecular mechanisms of convulsive syndromes of different etiologies.

Keywords: memantine, IEM-1921 (1-phenylcyclohexylamine), convulsion models, NMDA blockers, epilepsy.

The common final stage in convulsive syndrome is an excess of rhythmic activity of motor cortex neurons. The initial points in the development of this stage can be located in different brain structures and can be the targets of different etiological factors. The pathways of the pathogenesis of convulsions from target to appearance of intense electrical spike activity in the motor centers are also various. The main approaches to studying the pathogenesis of epilepsy and identification of the molecular mechanisms underlying it and seeking anticonvulsive agents include experimental models of convulsive states [20].

The clear multiplicity in the nosological forms of human epilepsy dictates the need to use and compare different models of convulsive states induced in animals. The role of convulsants, i.e., actions provoking transient (convulsive seizures) or prolonged recurrent convulsive states, can be played by many chemical agents with different mechanisms of action, as well as electrical stimulation. Depending on the intensity and duration of action, these produce increased convulsive readiness and/or active convulsive foci detected by neurological observations of experimental animals,

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TABLE 1. Assessment of the Phases of Convulsive Reactions in Response to Pentylenetetrazole, Points

Phases of convulsive reactions in rats in response to pentylenetetrazol	Points
No response	0
Twitching of ears and whiskers	1
Separate convulsive waves spreading along the axis of the trunk	2
Waves of motor activity with marked myoclonic convulsions without loss of posture (retained ability to stand)	3
Single generalized clonic-tonic convulsions with falling (loss of posture) (less than 1 min)	4
Prolonged (more than 1 min) or repeated generalized clonic-tonic convulsions with falling (loss of posture)	5
Death	Death

recording of electrical activity in different brain structures and neural networks, and morphological studies.

Among these models, there is significant interest in increased convulsive readiness resulting from genetic factors. Thus, generalized reflex responses to sound stimuli are seen in 10–15% of the population of Wistar laboratory rats [8]. Selection has yielded inbred rat strains with high (reaching 100%) audiogenic convulsive readiness, such as Krushinskii–Molodkina (KM) [8], genetically epilepsy-prone rat (GEPR) [11, 16], Ihara's genetically epileptic rat (IGER) [34], and Wistar audiogenic rat (WAR) [14, 21, 22]. These rats respond to sound stimuli with clonic-tonic convulsive seizures reminiscent of epileptic seizures in human [8, 16].

Comparison of the characteristics of epileptiform syndromes of different etiologies but similar in terms of neurological picture can be used to identify the details of the mechanisms of action of the arsenal of medications used in clinical practice and experimentally to prevent and cure seizures [30]. The results of such studies help in the search for new and effective anticonvulsants.

There is interest in studying convulsive readiness in KM rats in responsible to administration pentylenetetrazol, one of the most widely used convulsants in experimental practice. It is known that KM rats can, throughout the normal lifetime of Wistar rats (more than two years), survive frequent audiogenic tonic-clonic convulsive seizures, while about 50% of Wistar rats not selected for sensitivity to sound die after convulsive seizures of analogous intensity induced by pentylenetetrazol.

Glutamatergic synaptic transmission has an important role in the pathogenesis of convulsive states. Increased levels of glutamate secretion by nerve terminals or inhibition of reuptake pathways by glial cells leads to a shift in the balance between excitation and inhibition, promoting rhythmic activity of executive neurons. Studies using different experimental models have identified the undoubted involvement of NMDA glutamate receptors in this process, as well as the corresponding anticonvulsant activity of NMDA receptor blockers, particularly memantine [28] and IEM-1921 [5, 7, 9].

The aims of the present work were to compare the neurological manifestations of the actions of pentylenetetrazol in Wistar and KM rats, i.e., to identify the contribution of genetically determined audiogenic convulsive readiness, and to evaluate the ability of NMDA receptor blockers memantine and IEM-1921 to prevent the actions of pentylenetetrazol in KM rats.

METHODS

Experiments use male and female Wistar and Krushinskii–Molodkina (KM) rats with genetic predisposition to audiogenic convulsions. Mean body weight was 114 ± 3 g and animals were 5–6 weeks old. Rats were kept in the animal house with free access to feed and water. As rats are more active in the evening hours, experimental conditions were standardized and the spread of the results was reduced by performing all experiments at the same time of day, from 11:00 to 14:00.

Two days before experiments started, the ability of Krushinskii–Molodkina rats to respond to sound stimuli consisting of sine-wave tones of frequency 8 kHz and intensity 90 dB with convulsive seizures was verified. Sound was stopped when seizures reached the maximum level (usually within 2 min). Rats responding to sound with generalized clonic-tonic convulsive seizures were selected for further studies [1].

Experimental convulsions were induced in rats of both strains using i.p. pentylenetetrazol at a dose of 70 mg/kg. The results of this series of experiments (19 Wistar rats and 22 KM rats) served as controls for experiments on KM rats testing the anticonvulsant actions of two noncompetitive NMDA ionotropic glutamate receptor blockers: IEM-1921 [9, 31] and memantine [23]. Group 1 consisted of 22 rats which received i.m. IEM-1921 (5 mg/kg) 30 min before i.p. pentylenetetrazol (70 mg/kg); group 2 (10 rats) received i.m. memantine (5 mg/kg) 60 min before i.p. pentylenetetrazol (70 mg/kg).

The total duration of the observation period after administration of convulsant was 30–40 min in all experi-

ments, and continuous video recordings were made throughout this period. Subsequent analysis of these recordings yielded chronometric data for all phases of convulsive seizures. The animals' state was assessed using a previously developed points scale for the pentylenetetrazol model of convulsive states (Table 1). The maximal points scores reached by the animals were averaged by group and used as an indicator of the mean intensity of convulsive reactions in the group. The latent period of reaching the different phases of convulsive seizures was measured in each rat, along with the number of seizures and the durations of myoclonic and generalized clonic-tonic convulsions. All measures in the control and experimental groups were compared using Student's *t* test. Data are presented as mean ± standard error of the mean.

Experiments used pentylenetetrazol (Sigma) and memantine (ICN); 1-phenylcyclohexylamine (IEM-1921) was synthesized by V. E. Gmiro at the Research Institute of Experimental Medicine, Russian Academy of Medical Sciences.

RESULTS

The responses of rats of the two strains to i.p. administration of 70 mg/kg pentylenetetrazol were similar. During the latent period of 1–4 min, rats showed twitching of the ears and whiskers. This was followed by the occurrence of individual convulsive waves, spreading along the axis of the trunk, which was followed in turn by a sharp increase in locomotor activity with marked myoclonic convulsions without loss of posture. The next phase in the convulsive reaction consisted of single generalized clonic-tonic convulsions lasting less than 1 min, during which the animal fell onto its side. The response to pentylenetetrazol in some rats was restricted to one such seizure. Other animals responded to administration of pentylenetetrazol with multiple seizures of increasing durations. This state could lead to death. The points scale presented in Table 1 was used for quantitative analysis of the sequence of stages of the reaction to pentylenetetrazol.

No qualitative differences were seen in the neurological pattern of the actions of pentylenetetrazol in Wistar and KM rats. At the same time, convulsive readiness characteristic of KM rats was apparent in that their convulsive manifestations were significantly more marked than in Wistar rats and that death of animals at the same pentylenetetrazol dose were 2.1 times more frequent (Fig. 1).

There were no significant differences in the durations of the latent periods of the phases of the convulsive picture; the durations of the myoclonic components and generalized clonic-tonic seizures were also equal. Thus, the structure of individual seizures was identical in the two strains, though the severity of the convulsive state in KM rats was clearly greater (Table 2).

These results provide the background for the main part of the present study. Its aim was to compare the abilities of two noncompetitive blockers of NMDA-type ionotropic

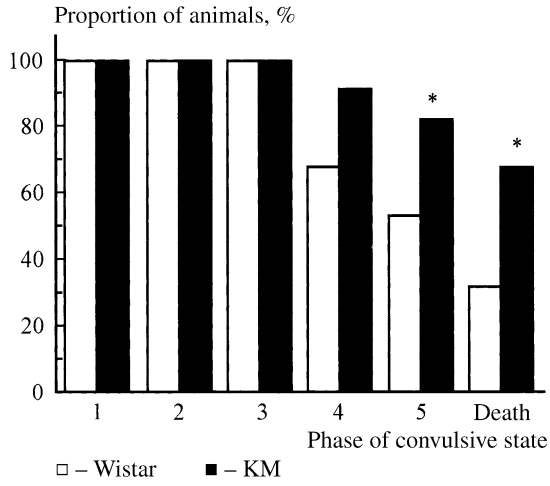

Fig. 1. Distribution of Wistar (n = 19) and KM (n = 22) rats in terms of phases of convulsive seizures evoked by pentylenetetrazol (70 mg/kg). *Significant differences between Wistar and KM rats (phases of convulsive seizures are shown in Table 1). For further detail see text.

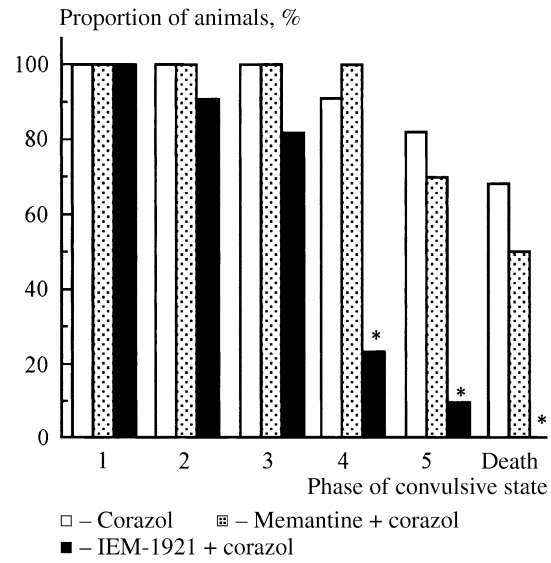

Fig. 2. Distribution of KM rats by phase of convulsive seizures in controls (n = 22) after memantine (n = 10) and IEM-1921 (n = 22). *Significant differences between the control group of rats and groups given an NMDA blocker (phases of convulsive seizures are shown in Table 1). For further detail see text.

glutamate receptors – memantine and IEM-1921 – to weaken the convulsive manifestations of the actions of pentylenetetrazol in KM rats.

The same blocker dose – 5 mg/kg – was selected (molecular weights were virtually identical) for both agents; this dose has previously been determined in experiments in the pentylenetetrazol model in mice and audiogenic convulsions in KM rats [2, 6]. Blockers were given i.m. at 30 min

TABLE 2. Comparison of the Severity of Convulsive Seizures in Wistar and KM Rats in Response to Pentylenetetrazole (70 mg/kg)

Parameter	Wistar, $n = 19$	KM, $n = 22$	t test	p
Mean intensity of convulsive reactions (1-5 points)	4.2 ± 0.2	4.8 ± 0.2	2.34	< 0.05
Latent period of development of convulsive reactions (2 points), min	1.5 ± 0.3	3.4 ± 1.2	1.43	> 0.05
Latent period of development of convulsive reactions (3 points), min	2.7 ± 0.7	3.8 ± 1.3	0.76	> 0.05
Latent period of development of convulsive reactions (4 points), min	1.9 ± 0.8	2.2 ± 0.5	0.24	> 0.05
Mean duration of myoclonic convulsions, sec	11 ± 4	36 ± 20	1.45	> 0.05
Mean duration of generalized convulsions, sec	535 ± 120	615 ± 125	0.45	> 0.05
Mean number of myoclonic convulsions	1.2 ± 0.1	1.4 ± 0.2	0.95	> 0.05
Mean number of generalized convulsions	1.8 ± 0.1	1.8 ± 0.2	0.31	> 0.05
Lethality, %	32	68	2.45	< 0.05

TABLE 3. Effects of Memantine (5 mg/kg) and IEM-1921 (5 mg/kg) on the Severity of Convulsive Seizures Induced in KM Rats by Pentylenetetrazole (70 mg/kg)

Parameter	Control, $n = 22$	Memantine, $n = 10$	IEM-1921, $n = 22$	Different between agents, p
Mean intensity of convulsive reactions	4.8 ± 0.2	4.7 ± 0.2	3.0 ± 0.2**	< 0.001
Latent period of development of convulsive reactions (2 points), min	3.4 ± 1.2	1.0 ± 0.2	2.1 ± 0.4	> 0.05
Latent period of development of convulsive reactions (3 points), min	3.8 ± 1.3	1.2 ± 0.3	4.6 ± 1.7	> 0.05
Latent period of development of convulsive reactions (4 points), min	2.2 ± 0.5	1.3 ± 0.3	4.4 ± 1.3	> 0.01
Mean duration of myoclonic convulsions, sec	36 ± 20	33 ± 17	65 ± 18	> 0.05
Mean duration of generalized convulsions, sec	615 ± 125	274 ± 83*	15 ± 9*	> 0.05
Mean number of myoclonic convulsions	1.4 ± 0.2	1.8 ± 0.3	2.2 ± 0.3	> 0.05
Mean number of generalized convulsions	1.8 ± 0.2	1.7 ± 0.2	1.3 ± 0.3	> 0.05
Lethality, %	68	50	0**	< 0.001

Notes. Differences from control: *$p < 0.05$, **$p < 0.01$.

(IEM-91921) and 60 min (memantine) prior to administration of pentylenetetrazol, as previous studies have shown that the preventive action of memantine develops more slowly [1]. Both blockers demonstrated the ability to weaken convulsive reactions to administration of pentylenetetrazol, though the action of memantine was very minor in terms of most measures. Mean convulsive reaction intensity was the same as in controls and the only significant reduction was in the total duration of generalized convulsive seizures, which was accompanied by a tendency to a decrease in deaths after convulsive seizures. The prophylactic action of IEM-1921 was much stronger (Fig. 2, Table 3). The mean intensity of convulsive seizures decreased almost two-fold and the total duration of generalized seizures decreased 41-fold. IEM-1921 completely prevented deaths, while memantine produced only a tendency to decreased lethality (68% in controls, 50% with memantine). Attention is drawn to the fact that the more "severe" phases of convulsive reactions to pentylenetetrazol, i.e., the clonic-tonic convulsive seizure, was evaluated at 4–5 points, leading to death in a significant proportion of rats (Fig. 2, Table 3). The probability of myoclonic convulsions and the duration of this period were essentially identical to those in control animals.

DISCUSSION

KM rats, which are characterized by a stable and high level of sensitivity to sound, were produced by selection for many years – starting in 1947 [8]. These animals respond to sufficiently intense and prolonged sound stimuli with typical generalized clonic-tonic convulsive seizures, which can

be repeated several times but do not generally lead to death. It can be suggested that KM rats are in a state of elevated genetically determined convulsive readiness. This raises the question of whether this state is selective in relation to sound stimuli or propagates to other convulsion-provoking factors. This was tested using a model of pentylenetetrazol-induced convulsions, this being widely used in the search for new antiepileptic substances [24]. Pentylenetetrazole (corazol) is an analeptic which was previously used for the convulsive therapy of manic-depressive psychoses and schizophrenia, and which when given to experimental animals can induce convulsions or increase the sensitivity of the animals to convulsive treatments of different types. In terms of pathogenetic mechanism, the pentylenetetrazol convulsion model is the closest to several forms of epileptogenesis in humans (generalized absences and myoclonic convulsions) [25]. The mechanism of action of pentylenetetrazol is linked with its ability to weaken GABAergic synaptic transmission, thus suppressing $GABA_A$ and metabotropic $GABA_B$ receptors [12, 13]. This weakening of inhibitory processes evidently promotes the development of convulsive syndrome.

These experiments on Wistar and KM rats showed that the high convulsive readiness of KM rats significantly increases the severity of convulsive seizures induced by i.p. pentylenetetrazol. This is consistent with data obtained in experiments on rats of other rat strains with increased sensitivity to the convulsant action of sound [26, 32, 33]. In our experiments, administration of pentylenetetrazol in KM rats was followed by faster (compared with Wistar rats) onset of seizures and a greater proportion of animals achieving the "severe" phases of seizures (4 and 5 points), with generalized clonic-tonic convulsions and increased death rates (32% in Wistar, 68% in KM).

This raises the following questions: What is the nature of the additivity of the convulsive state of audiogenic KM rats and the convulsant action of pentylenetetrazol? At what level of structures and pathogenetic mechanisms does this interaction occur? The pathogenesis of audiogenic convulsions in KM rats is not clear in all its details. More detailed reports have appeared on the pathogenesis of audiogenic convulsion in rats of other strains [17, 22, 29]. There are grounds for considering that the source of genetically determined increases in sound sensitivity in most cases consists of the auditory nuclei, while the inferior and then the superior colliculi, medial geniculate body, and amygdala play an important role in maintaining this state [8, 17, 19, 26]. In addition, audiogenic rats showed some functional insufficiency of the GABAergic inhibitory system and some increase in the excitability of hippocampal neurons [15, 35].

Electroencephalographic data and fMRI results have shown that the anterior nuclei of thalamus and their interaction with the cortex play an important role in the genesis of convulsions to pentylenetetrazol [10, 27]. In addition, realization of myoclonic convulsions involves most limbic structures, including the hippocampus, which have tight connections with the anterior nuclei of the thalamus. Pentylenetetrazole induces neuron and glial cell death in the hippocampus [18], along with demyelination in the cortex and hippocampus [36].

The relative similarity in the features of convulsive seizures induced by sound stimuli in KM rats, administration of pentylenetetrazol to Wistar rats, and administration of pentylenetetrazol to KM rats may be evidence for the common nature of the molecular mechanisms of these pathological reactions.

The ability of the NMDA glutamate receptor blockers IEM-1921 and memantine to prevent convulsive manifestations has been demonstrated by our studies using a number of models in experiments on mice and rats. Thus, IEM-1921 was found to prevent convulsions induced by administration of NMDA into the cerebral ventricles in mice [5, 7]. IEM-1921 and memantine were able to prevent acute convulsions in mice in response to administration of pentylenetetrazol or arecoline [3, 6], and could also slow or weaken the development of pentylenetetrazol kindling [4]. Both blockers prevented convulsive seizures induced by sound stimulation in KM rats [1, 2].

Supporting the view that NMDA receptors not only have a role in the pathogenesis of convulsive seizures induced by sound stimuli in KM rats, but are also involved in forming increased convulsive readiness is the high efficacy of IEM-921 in relation to seizures induced by administration of pentylenetetrazol. Administration of agent (5 mg/kg) 30 min before pentylenetetrazol significantly weakened the mean intensity of convulsive seizures and completely prevented deaths, while 68% of "untreated" rats died during the first hour of the observation period. In analogous experiments, memantine was much less effective. At a dose of 5 mg/kg, it produced no more than a tendency to a weak anticonvulsive effect and did not prevent deaths of rats after generalized clonic-tonic convulsive seizures.

The results obtained here provide evidence that NMDA-type glutamate receptors play an important role in the molecular mechanisms producing convulsive syndromes of different etiologies. Blockers of the open ion channels of these receptors may find use as substances able to resolve convulsive seizures and the state of convulsive readiness.

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