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Behavioural studies with a newly developed neuroprotective KYNA-amide

Levente Gellért · Dániel Varga · Marian Ruszka · József Toldi · Tamás Farkas · István Szatmári · Ferenc Fülöp · László Vécsei · Zsolt Kis

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Abstract The neuroactive properties and neuroprotective potential of endogenous L-kynurenine, kynurenic acid (KYNA) and its derivatives are well established. KYNA acts as an antagonist on the obligatory co-agonist glycine site, and has long been at the focus of neuroprotective trials. Unfortunately, KYNA is barely able to cross the blood–brain barrier. Accordingly, the development and synthesis of KYNA analogs which can readily cross the BBB have been at the focus of research interest with the aim of neuroprotection. Earlier we reported a new KYNA-amide crosses the BBB and proved neuroprotective in several experiments. In the present study, we investigated the locomotor activity, working memory performance, and also the long-lasting, consolidated reference memory of animals treated intraperitoneally (i.p.) with the novel analog. The effects of the novel analog on the spatial orientation and learning ability of rats were assessed in the Morris water maze (MWM) paradigm. The effects on locomotor activity of mice was assessed in the open field (OF) paradigm, and those on the spatial orientation and learning ability of mice were investigated in the radial arm maze (RAM) paradigm. It emerged that there is a dose of this KYNA-amide which is neuroprotective, but does not worsen the cognitive function of the brain. This result is significant in that a putative neuroprotectant without adverse cognitive side-effects is of great benefit.

Kex words Behavioral studies · Mice · Rat · Open-field · Water maze · Radial maze

L. Gellért · D. Varga · J. Toldi (✉) · T. Farkas · Z. Kis
Department of Physiology, Anatomy and Neuroscience, University of Szeged, Közép fasor 52, Szeged 6726, Hungary
e-mail: toldi@bio.u-szeged.hu

M. Ruszka · L. Vécsei
Department of Neurology, University of Szeged, Semmelweis u. 6, Szeged 6725, Hungary

I. Szatmári · F. Fülöp
Institute of Pharmaceutical Chemistry and Research Group for Stereochemistry, Hungarian Academy of Sciences, University of Szeged, Eötvös u. 6, Szeged 6720, Hungary

Introduction

Brain damage resulting from cerebral ischemia is at least partly related to the *N*-methyl-D-aspartic acid (NMDA) receptors, which mediate an excessive entry of Ca^{2+}, initiating ischemia-induced excitotoxicity (Dirnagl et al. 1999; Endres and Dirnagl 2002).

The aim of acute intervention against excitotoxicity is, therefore, to inhibit the overactivated NMDA receptors (Prass and Dirnagl 1998). Examinations usually focus on the pyramidal cells of the CA1 hippocampal subfield because they are particularly vulnerable to an ischemic insult and selectively die after global forebrain ischemia (Schmidt-Kastner and Freund 1991). Vulnerability is related to the high density of NMDA receptors. Although several NMDA antagonists have proven to be robust neuroprotectants, many failed in clinical trials due to their adverse side-effects, such as psychotomimesis, respiratory depression or cardiovascular dysregulation (Muir 2006). Indeed the acute effects of massive non-competitive NMDA antagonism lead to unacceptable symptoms (Gunduz-Bruce 2009).

In human and murine both NMDA and alpha-7 nicotinic receptors are highly concentrated in the hippocampus. Integrity of these receptors is required to several cognitive functions, e.g. learning and memory storage (Bliss and Collingridge 1993) and their function can be measured, e.g.

with orientation tasks. Disruption of the hippocampal and striatal glutamergic and cholinergic transmission results in a decreased spatial orientation and learning performance (Butelman 1989; Ohno et al. 1993, 1994; Nakazawa et al. 2004; Yoshihara and Ichitani 2004; Surmeier et al. 2009).

Neuroactive properties and neuroprotective potential of "L-kynurenine (KYN)" and "kynurenic acid (KYNA)", and derivatives are well established. (Stone 2000; Wu et al. 2000; Schwarcz and Pellicciari 2002; Stone and Addae 2002; Vamos et al. 2009a, b; Zadori et al. 2009).

Kynurenic acid is an endogenous antagonist of the strychnine-insensitive glycine-binding site of the NMDA receptor, a weak antagonist of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) (Prescott et al. 2006) and kainate receptors (Kenton et al. 1990) and also an inhibitor of the alpha-7 nicotinic receptor (Hilmas et al. 2001), which is involved in the presynaptic regulation of L-glutamate. Considering these properties, KYNA or synthetic derivatives may not only attenuate overactivated glutamate receptors but also could worsen physiological glutamergic and cholinergic function as well. Indeed, behavioural effects of exogenous KYN and KYNA are reported (Potter et al. 2010; Vecsei and Beal 1990; Erhardt et al. 2004; Rassoulpour et al. 2005; Chess and Simoni 2007).

Recently, development and synthesis of KYNA analogs which can easily cross the blood–brain barrier (BBB) are in the focus of research with the aim of neuroprotection.

In the present study, we set our focus on the behavioural effects of a novel KYNA amide 2-(2-*N*,*N*-dimethylaminoethylamine-1-carbonyl)-1H-quinolin-4-one hydrochloride (Fig. 1) (Fulop et al. 2009), which proved to be neuroprotective in our former studies. However, detailed behavioural studies of this novel KYNA amide have not carried out yet. In this study, we investigated locomotor activity, working memory performance, and also the imprinting and retrieval of long lasting, consolidated reference memory of the animals, treated intraperitoneally (i.p.) with either vehicle or the novel analog. Effect of the novel analog on spatial orientation and learning ability of rats was assessed in the Morris water maze (MWM) paradigm. Effect on locomotor activity of mice was assessed in the open field (OF) paradigm. Effect on spatial orientation and learning ability of mice was investigated in the radial arm maze (RAM) paradigm.

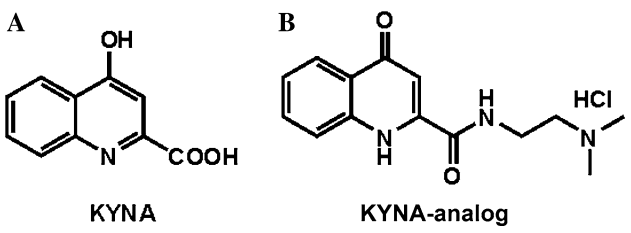

Fig. 1 Structures of kynurenic acid (**a**) and the novel analog: 2-(2-*N*,*N*-dimethylaminoethylamine-1-carbonyl)-1H-quinolin-4-one hydrochloride (**b**)

Materials and methods

Open field and radial arm maze

For the open field and radial arm maze tests 9 to 16-week-old male CFLP mice were used. The animals were housed under standard laboratory conditions, in groups of 5, at constant temperature and humidity, under an inverse 12-h dark/light cycle, with *ad libitum* access to food and tap-water. For radial arm maze test, subjects were partially deprived of food. Their averaged body weight was reduced gradually and maintained at 85–90% of free-feeding body weight. During this period, animals were habituated to the radial maze and the inverse dark/light cycle.

Designing the open field

The open field was a square arena in a ground-space of 50 × 50 cm.Walls were opaque (light grey, so that animals cannot see the room) and 50 cm high. Arena floor was not completely smooth that would not enable animals to move freely.

Experimental protocol

Mice ($n = 10$ per groups) were removed from their home cage, gripping the tail and were placed into the middle of one side of the arena facing the wall. Animals were allowed to move freely for 5 min. Following the experimental session, mice were removed carefully from the open field arena, and placed in its home cage. Apparatus was wiped clean with 50% alcohol after each experimental session to avoid olfactory cueing.

Designing the radial arm maze

The maze consisted of a central platform 24.5 cm in diameter, with eight enclosed arms radiating outwards. Each arm was 38 cm in length, 9 cm in width and 20 cm in height with transparent plastic side walls. Food cups were located at the end of each arm.

Experimental protocol

During the habituation period, each animals were handled and placed in the maze for 4 min. Food pellets were scattered throughout the maze. Thereafter, food pellets were moved systematically toward the food cups. At last only the food cups were baited.

Animals were habituated to the maze for 2 weeks described above. At the end of this period, we introduced the four of eight arms baited paradigm. From that time every second arm was baited. The animal was placed into the central platform and was allowed to move freely in the maze and to find the pellets. The session ended when the animal found the food in all arms or after 4 min. Apparatus was wiped clean with 50% alcohol after each experimental session to avoid olfactory cueing.

In the "imprinting" test, we assessed the performance of the animals ($n = 10$–12 per group) for eight consecutive days.

The performance of the animals was assessed as follows:

Reference memory error was considered as first entry into the non-baited arms (one entry per arm was considered, therefore, the maximum number of entries can be 4).

Total error was considered as entry into the non-baited arms.

Working memory error was considered as re-entry into a baited arm.

Total Time was considered as time elapsed until finding the food in all four arms.

Morris water maze

For Morris water maze, male Wistar rats ($n = 10$) weighing 250–300 g were used. The animals were housed under standard laboratory conditions, in groups of 5, at constant temperature and humidity, under a inverse 12-h dark/light cycle, with *ad libitum* access to food and tapwater. Animals were habituated to the inverse dark/light cycle and to the water maze for 2 weeks.

Designing the Morris water maze

Spatial learning was assessed in a circular tank (diameter 1.6 m; depth 0.6 m) containing 0.35 m deep water at room temperature. The water was made opaque by adding 10 ml of blue distemper in order to prevent the animals from seeing the submerged platform. Rats were expected to locate an escape platform (diameter 8 cm) submerged 1.5–2 cm below the surface of the water. Platform was located always in the middle of the same goal quadrant during the whole experiment. Except the goal quadrant, in the middle and at the border of the quadrants five starting point was allocated on the perimeter of the tank.

Experimental protocol

During habituation period, animals were released daily in the water always facing the wall from arbitrarily allocated starting points. Animals were allowed to locate the platform for 60 s. If a rat failed to solve the task within 60 s, it was guided there by the experimenter Animals were always allowed to stay on the platform for 20 s to orient themselves in space.

After habituation period, the acquisition period was performed on seven consecutive days. During acquisition period on rats, two probes were performed. Pre-training probe was performed as first swim without platform immediately before the five-trials block of training. Another post-training probe was performed immediately after the five-trials block of training without platform.

Escape latency was considered as the time elapsed to locate the platform from arbitrarily allocated starting points in the first training trial. Summerized escape latency was considered as time elapsed to locate the platform (mean of five-trial training with platform). Preference for goal quadrant was considered as time spend at the goal quadrant related to adjacent and cross quadrants (pre-and post-trial probes without platform).

To facilitate spatial orientation prominent visual cues were located on the room walls (e.g. wall posters, electrical fittings). Two incandescent lamps suspended above the apparatus, and shielded by a white plexiglas sheet supplied dim light. A low intensity white noise was emitted from an airing ventilator. Mooving path of the animals was registered with SMART video tracking system.

Principles of animal care (NIH publications No. 85–23), and the protocol for animal care approved by both The Hungarian Health Committee (1998) and the European Communities Council Directive (86/609/EEC) were followed.

Drug administration

In the water maze test, we did not use separate control and analog treated groups. Instead, on the 6th day of the acqusition period we treated the animals with 1.5 ml of vehicle (0.1% PBS) intraperitoneally. On the 7th day, we treated the animals with 1 mmol ($\sim$300 mg/bodyweight kg) of the analog intraperitoneally (dissolved in 0.1% PBS).

In the open field test, animals received vehicle 1 and 2 mmol of the analog, respectively, (dissolved in PBS) i.p. 1 h before the trial. In the radial maze imprinting test, animals received daily vehicle and 1 mmol of the analog (dissolved in PBS) i.p. 1 h before the trial. For all the series of experiment, we used separate groups of animals. At the end of the experiments, animals were killed by applying a lethal dose of urethan administered i.p.

Statistical analyses

The result of all tasks was expressed as means $\pm$ S.E. The distribution of the data was tested with the Shapiro-Wilk

normality test. The sphericity of the data was tested with the Levene test. For multiple comparisons, we applied One-Way ANOVA with Dunett T3 post-hoc test.

For repeated measures, we used non-parametric Friedman-test. For repeated measures with factors treatment and days, we used generalized linear model/generalized estimating equation (Glm/Gee), an extended repeated measures ANOVA for special cases, see: Ballinger (2004). Results were computed with the PASW Statistics 18 data analysis package (SPSS Inc. Chicago, USA). Results were plotted with Origin 7.0

software (OriginLab Corporation, Northampton, MA, USA).

Results

Water maze

Significant preference for the goal quadrant could not be observed in the pre-training probe on days 5th, and 6th. Suprisingly on the 7th day preference for the goal quadrant increased significantly compared to the all other quadrants (Fig. 2a; $p \leq 0.02$ to all quadrants).

By the 5th day significant decrease of escape latency occured ($p = 0.01$). On the 6th (treatment with vehicle i.p.) and 7th (treatment with 1 mmol of the analog i.p.) days performance developed marginally further. Neither vehicle

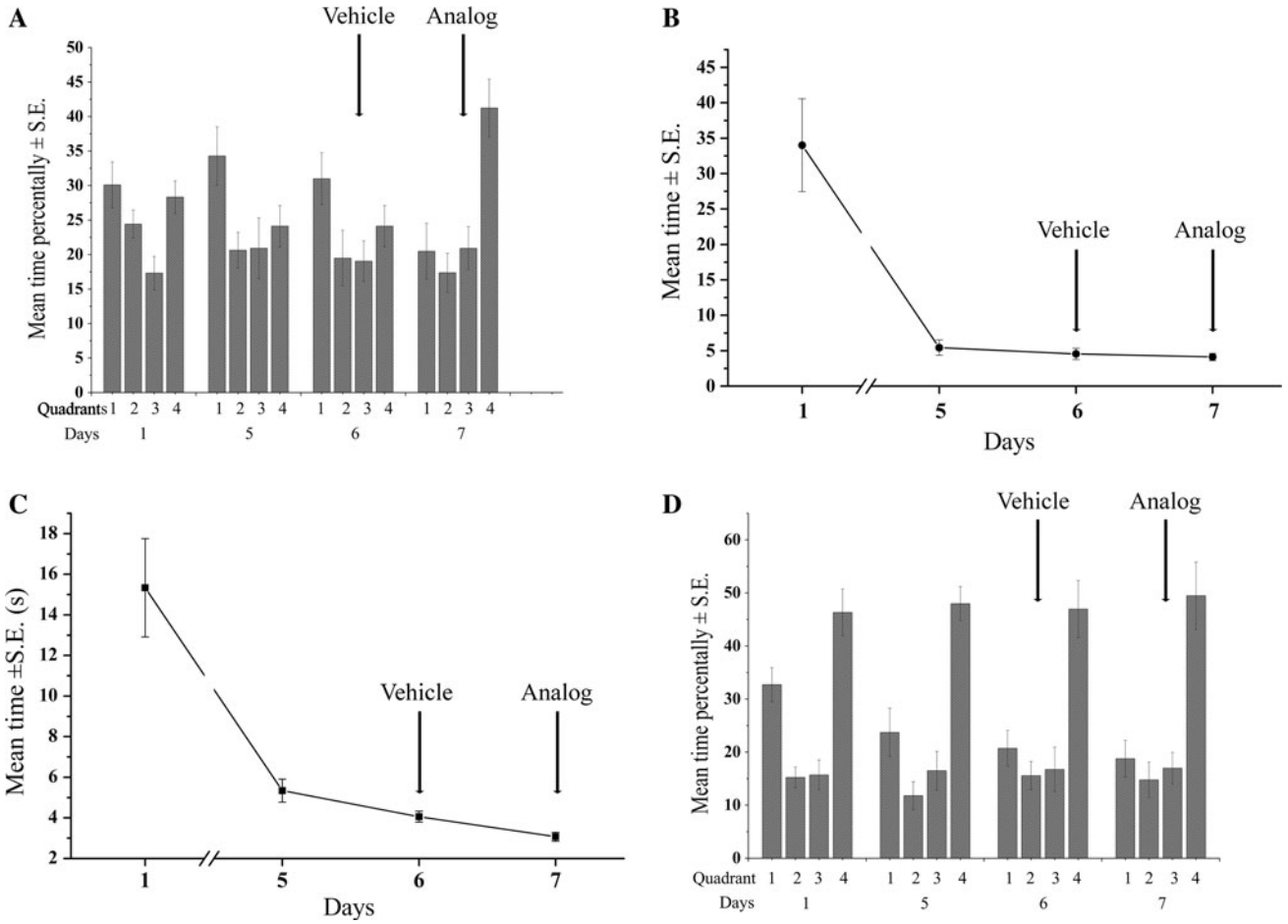

Fig. 2 **a** Pre-training zone preference and reference memory performance. Time spent in each quadrant on the first 5th, 6th and 7th days is expressed as percentage of 60 s free swimming whitout platform (mean ± S.E.). *Coloumns* represent the quadrants, coloumn 4 is the goal quadrant. Significant increase for the goal quadrant emerged on the 7th day ($p \leq 0.02$ to all quadrants), as animals were treated with 1 mmol of the analog i.p. **b** Escape latency. Mean time elapsed to locate the platform in the first training trial on the first 5th, 6th and 7th days (mean ± S.E.). By the 5th day significant decrease of escape latency occured ($p \leq 0.001$). **c** Summerized escape latency. Mean time elapsed to locate the platform during the five-trial training with platform on the first 5th, 6th and 7th days (mean ± S.E.). Significant decrease of summerized escape latency occured on the 6th (treatment with vehicle i.p.) day. **d** Post-training working memory performance. Time spent in each quadrant on the first 5th, 6th and 7th days is expressed as percentage of 60 s free swimming without platform (mean ± S.E.). Columns represent the quadrants, column 4 is the goal quadrant. Significant preference for the goal quadrant emerged on every day ($p \leq 0.008$ to all quadrants)

nor analog treatment worsened the performance on days 6th and 7th (Fig. 2b; $p = 001$).

Reference memory was also considered as the summerized mean escape latency of training trials. In this sense escape latency was decreased gradually, best performance could be observed on the 6th and 7th day (Fig. 2c; $p = 0.001$). On the 7th day (treatment with 1 mmol of the analog i.p.) performance developed marginally further. Neither vehicle nor analog treatment worsened the performance on days 6th and 7th.

Working memory performance was considered as daily post training probe. Preference for goal quadrant was significantly higher on every day (Fig. 2d; $p \leq 0.008$ to all quadrants), working memory was built-up successfully. The most balanced performance was observed on days 6th and 7th.

In conclusion, treatment with either vehicle or 1 mmol of the analog did not worsen the performance of the animals.

Radial arm maze

By 6th day of the radial maze imprinting test, the number of reference memory errors decreased significantly

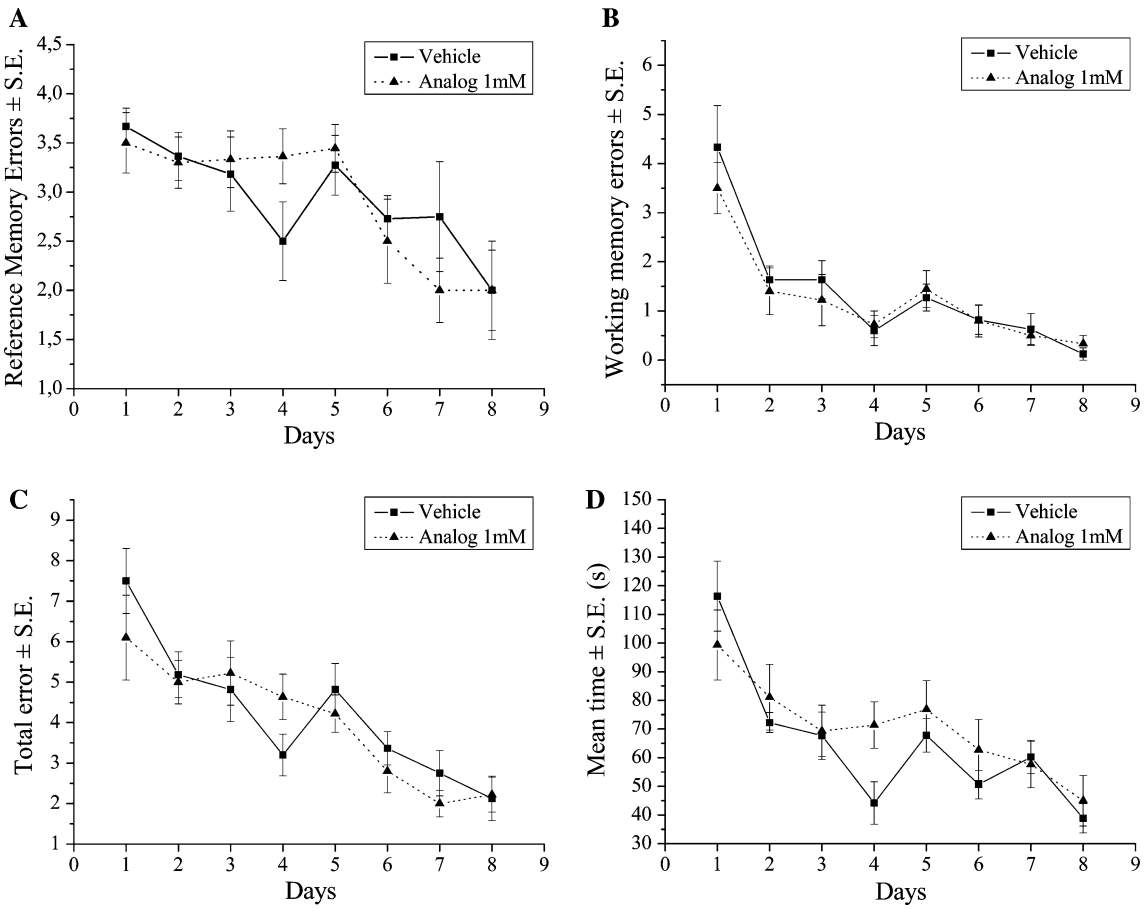

Fig. 3 **a** Reference memory error. Number of reference memory errors during radial maze imprinting test (mean ± S.E.). Number of errors decreased significantly in both vehicle (*solid line*) and analog (*dotted line*) treated groups by the 6th day ($p = 001$). Statistical analysis did not reveal significant difference in the performance of the two groups ($p = 0.523$). **b** Working memory errors. Number of working memory errors during radial maze imprinting test (mean ± S.E.). Number of errors decreased significantly in both vehicle (*solid line*) and analog (*dotted line*) treated groups by the second day ($p \leq 0.001$). Statistical analysis did not reveal significant difference in the performance of the two groups ($p = 0.356$). **c** Total errors. Number of total errors during radial maze imprinting test (mean ± S.E.). Number of errors decreased gradually during the whole experiment. Significant decrease occured on the third day ($p = 0.042$) in both vehicle (*solid line*) and analog (*dotted line*) treated groups. Statistical analysis did not reveal significant difference in the performance of the two groups ($p = 0.121$). **d** Time elapsed to solve radial maze task. Time elapsed until finding the food in all baited arms (mean ± S.E.). Time required to solve the task decreased significantly on the second day ($p \leq 0.001$)) in both vehicle (*solid line*) and analog (*dotted line*) treated groups. Statistical analysis did not reveal significant difference in the performance of the two groups ($p = 0.753$)

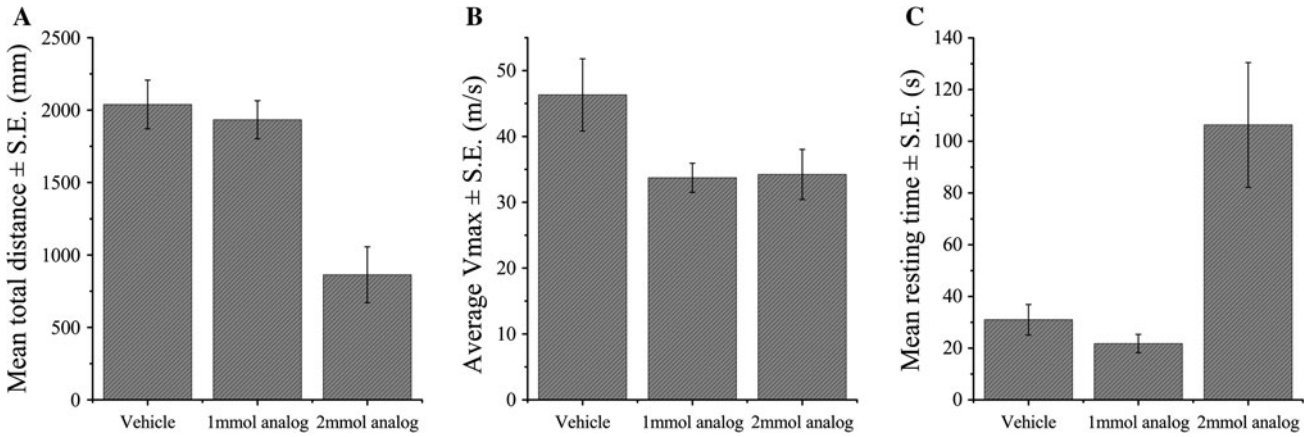

Fig. 4 **a** Total distance**.** Ambulation distance of certain groups in the open field (mean ± S.E.). Treatment with 1 mmol of the analog decreased ambulation marginally. However, treatment with 2 mmol of the analog resulted in a significant decrease of ambulation ($p = 0.001$). **b** Maximal speed. Maximal speed the animals reached in the open field (mean ± S.E.). Treatment with 1 and 2 mmol of the analog decreased tha maximal speed of the animals to the same level. However, the difference was not significant in any cases ($p = 0.069$). **c** Resting time. Time the animals spent with resting in the open field (mean ± S.E.). Treatment with 1 mmol of the analog decreased resting time marginally. However, treatment with 2 mmol of the analog increased the resting time significantly ($p = 0.035$)

(Fig. 3a, $p \leq 0.001$). Statistical analysis did not reveal significant difference between the two groups during the 8 days ($p = 0.523$).

Number of working memory errors decreased on the 2nd day significantly (Fig. 3b; $p \leq 0.001$) and the low error rate stayed steady. Statistical analysis did not reveal significant difference between the two groups during the 8 days ($p = 0.356$).

Number of total errors decreased significantly by the 3rd day (Fig. 3c; $p = 0.042$). This tendency could be observed on the rest of the days. Statistical analysis did not reveal significant difference between the two groups during the 8 days ($p = 0.121$).

Mean time elapsed to completing the task decreased significantly by the second day (Fig. 3d; $p \leq 0.001$) and decreased tendentially along. Oscillation can be observed in the performance of both the groups, however, both show a tendency to improve. Statistical analysis did not reveal significant difference between the two groups during the 8 days ($p = 0.753$).

In conclusion, we could not find significant difference between the improvement of the two groups in any of the cases.

Open field

Treatment with 1 mmol of the analog resulted in a marginal decrease in the ambulation of the animals. However, 2 mmol resulted in significant decrease of this parameter (Fig. 4a; $p = 0.001$).

Both 1 and 2 mmol of the analog decreased the maximal speed of the animals to the same level, however, difference was not significant (Fig. 4b).

Interestingly, 1 mmol of the analog decreased marginally the resting time of the animals, however, treatment with 2 mmol resulted in a significant increase of this parameter (Fig. 4c; $p = 0.035$).

Increment in stereotype behaviour could not be observed. Difference in preference for marginal or central zone of the open field did not emerge.

Discussion

NMDA blockade is a widely accepted neuroprotective strategy in the acute neuroprotection of the ischemic brain. Indeed severeal antagonist proved to be robust neuroprotectant (Muir 2006). KYNA an endogenous metabolites and its derivatives are in the focus of neuroprotective trials. Unfortunately, KYNA is barely able to cross the BBB. Therefore, development and synthesis of KYNA derivatives which readily cross the BBB is of great benefit. Recently, our novel KYNA analog, 2-(2-*N*,*N*-dimethylaminoethylamine-1-carbonyl)-1H-quinolin-4-one hydrochloride (Patent Application No: 104448-1998/Ky/me), proved to be neuroactive in several experimental paradigm. The analog effectively reduced c-fos (Knyihar-Csillik et al. 2008), and nNOS (Vamos et al. 2009a, b) activation in an experimental animal model of migraine, effects interpreted as due to NMDA blockade. Moreover, in a in vitro comparative electrophysiological study, this compound was found to have the same neuromodulatory attributes as kynurenic acid (Marosi et al. 2009). NMDA antagonism was also acknowledged. 1 mmol of the analog administered i.p. effectively reduces the amplitudes of hippocampal population spike (Nagy et. al.; unpublished). In our former study,

we showed that this compound is a robust neuroprotectant and attenuate damage to hippocampal CA1 pyramids in global cerebral forebrain ischemia in rats (Gellért et al. 2011).

Introducing this novel neuroprotectant the detailed analysis of the behavioural effect of this new compound seemed to be extremely important. In this study, we investigated the behavioural effects of the novel KYNA analog from several aspects.

In the Morris water maze task, we examined the effect of the novel analog on working memory and long lasting reference memory of rats. During the data acquisition period, animals performance developed significantly. As a result of treatment with 1 mmol of the analog, the performance did not worsen. A kind of anxiolytic effect of the analog emerged, animals were more calmed. Probably as a result of this phenomenon, animals solved the task more successfully.

To investigate the effect of the analog on mice preliminarily, we performed an open field test which measures the locomotor activity and exploratory drive. We found that 1 mmol of the analog do not influence significantly the exploratory activity of the animals. However, 2 mmol of the analog influences significantly the exploratory activity.

We also assessed the effect of the analog on spatial orientation and learning. In the radial arm maze imprinting test 1 mmol of the analog administerd before the daily sessions did not worsen the learning tendency compared to the control group.

As it was found before the new KYNA-amide crossed the BBB and proved to be neuroprotective in several experiments (cited above). However, the knowledge that exists a dose of this KYNA-amide which is neuroprotective but does not worsen the cognitive function of the brain, has a particular importance. Such properties (effective dose without adverse side-effects in cognitive function) may serve as a background to develop new neuroprotective agents.

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