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Effects of the alpha- and gamma-polymorphs of glycine on the behavior of catalepsy prone rats

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ABSTRACT

Glycine is used to treat various health problems and is efficient in the treatment of the negative symptoms of schizophrenia. Since glycine exists as a few polymorphs, the aim of this work is to compare the effects of the alpha- and gamma-forms of glycine on the behavior of the genetic catalepsy (GC) strain of rats. Both polymorphs of glycine have been administered to rats orally as pure solid chemicals, and cataleptic behavior and behaviors in the open-field, elevated plus-maze, and light–dark box tests were studied. Both the alpha- and gamma-polymorphs of glycine increased exploratory activity in the open-field test, but only the gamma-polymorph had beneficial effects on catalepsy and exploratory activity in the light–dark box and reduced anxiety in the elevated plus-maze.

1. Introduction

Glycine is used to treat various health problems, including ischemic stroke, anxiety, insomnia, opium addiction, alcohol intoxication, benign prostatic hyperplasia and others (Gusev et al., 2000, 2001; Komissarova and Nartsissov, 2001; Tsai et al., 2002; Padilla-Martin et al., 2009). In several publications, glycine has been considered to be efficient in the treatment of the negative symptoms of schizophrenia (Babić and Babić, 2009; Heresco-Levy et al., 1999; Javitt et al., 1994; Kaufman et al., 2009; Waziri, 1996). A difference in the biological effects of dissolved and solid (sublingual pills) forms of glycine has been emphasized (Gusev et al., 1999). These findings suggested that not only the chemical formula, but also the properties of the solid forms of glycine, such as crystal structure, particle size, supramolecular complexes with excipients in the formulation, among others, can be important for its biological activity. It has been well established that solid drugs with the same chemical composition of the active pharmaceutical ingredients may have different activities due to the differences in the characteristics of their solid formulation (Bernstein, 2002; Brittain, 1999; Hilfiker, 2006). Glycine in ambient conditions is known to exist as three polymorphs termed as α- (Marsh, 1958), β- (Iitaka, 1960), and γ-forms (Iitaka, 1961), which differ considerably in the crystal structures and physical properties (Boldyreva et al., 2003a, 2003b; Boldyreva, 2009; Bordallo et al., 2008; Iitaka, 1960, 1961). There are numerous reports concerned with the biological activity of glycine and its application in medicine. However, these publications do not even report, which of the polymorphs (or their mixture) have been used.

The aim of the work was to compare the behavioral effects of the α- and γ-forms of glycine. Once obtained, these two polymorphs can be preserved indefinitely in ambient conditions, and, therefore, both are suitable for preparing solid formulations. The crystal structures of the α- and γ-forms of glycine are very different: the head-to-tail chains of glycine zwitter-ions $^{+}NH_3$–CH_2–COO^{-} in the α-polymorph form double centrosymmetric layers, whereas they are linked into triple helices additionally connected in a three-dimensional network in the polar chiral structure of the γ-form (Fig. 1).

2. Materials and methods

2.1. Drugs

Glycine was purchased from Soyuzkhimreaktiv (Russia). It was recrystallized to obtain pure α- and γ-polymorphs, as described elsewhere (Boldyreva et al., 2003a). The samples were characterized by ATR FT-IR-spectra [the frequency range 4000–600 cm^{-1} at 4 cm^{-1}

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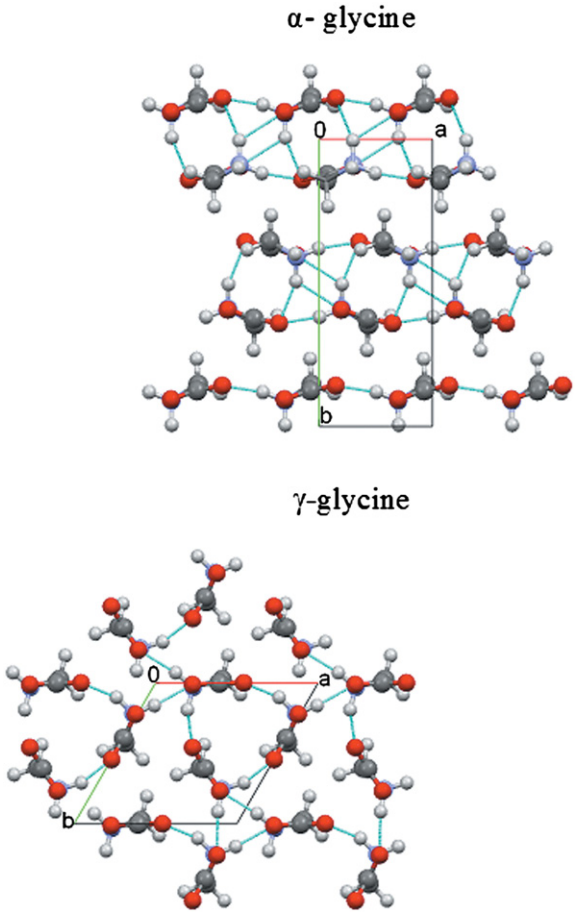

Fig. 1. Fragments of crystal structures of the α- and γ-polymorphs of glycine.

resolution, measured in the reflection mode using an FT-IR spectrometer Digilab Excalibur 3100 with a single reflection diamond ATR MIRacle device (Pike)], X-ray diffraction [Bruker D8-GADDS diffractometer, CuKα-radiation, λ = 1.54184 Å, Hi-STAR area detector], optical and scanning electron microscopy [the sample contained conglomerates of 50–70 μm formed by particles of 1–20 μm].

2.2. Animals

The GC rat strain was used in the experiments. This strain with propensity for catalepsy was developed at the Institute of Cytology and Genetics (Novosibirsk, Russia) by selection from a Wistar outbred population for predisposition to cataleptic reactions. Animals which demonstrate the catalepsy in each of the six tests were used for breeding (Barykina et al., 1983).

It was shown that predisposition to catalepsy in GC rats may be described by a dominant major gene inheritance with a 60% penetrance (Kolpakov et al., 1999). Within the range of cataleptic behavior, which refers to the prolonged maintenance of an enforced immobile posture (Fig. 2), GC rats are distinguished by a prolonged pinch-induced catalepsy (Kolpakov et al., 1999). Comparisons of the neurophysiological and neurochemical characteristics of GC rats and schizophrenic patients have revealed many similarities (Kolpakov et al., 1995, 1996, 1999). The GC strain was thus proposed as an animal model for the biological settings in which schizophrenia develops in humans (Kolpakov et al., 2004). The experiments involved 30 male GC rats. All the experimental rats were kept under standard conditions in the Animal Facility of the Institute of Cytology and Genetics. The rats were housed in groups of 4–5 per cage (cage size: 60 × 40 × 20 cm) under a natural light regime, with food and water given *ad libitum*. The experiments were conducted during the autumn season. At this time, the local monthly average length of daylight was approximately 10 h. A day before the experiments, each animal was put into an individual cage. At the onset of the experiments, the rats were 3–3.5 months old, weighing about 300 g. All procedures were carried out in accordance with the international guidelines for animal care and use (Ethical principles and guidelines for experiments on animals, Experientia 1995 Jan 15; 51(1):1–3).

2.3. Design of the experiments

The experimental animals were divided into three groups. The controls (n = 10) received placebo, another group (n = 10) α-glycine, and the third (n = 10) γ-glycine. Powdered glycine crystals (10 mg) were added to a piece of cheese (1–1.5 g), and the cheese with glycine was rolled into balls to be consumed by rats in the observer's presence. The control rats were given cheese alone. The animals received the drug (or cheese pellet) once a day.

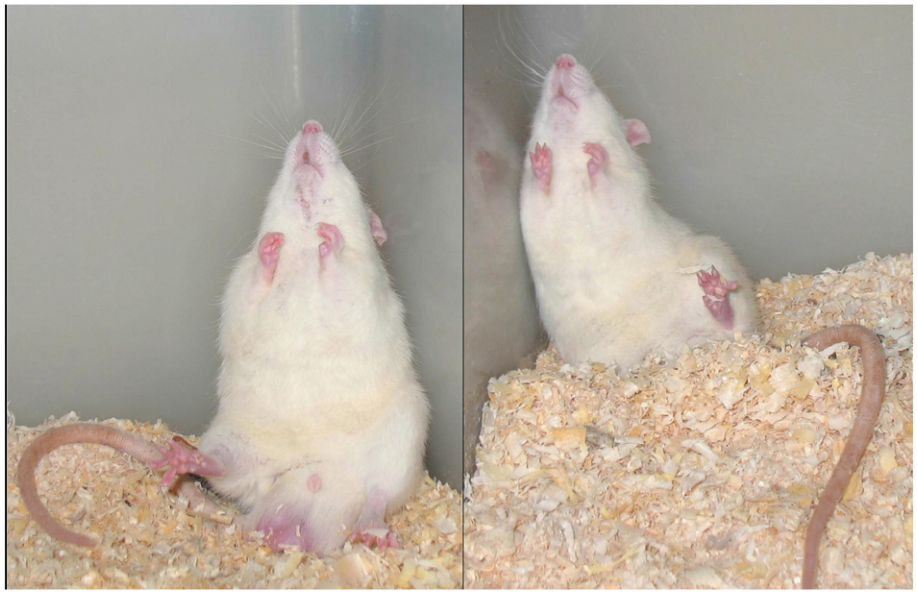

Fig. 2. GC rats in a typical cataleptic position induced by experimenter (see text).

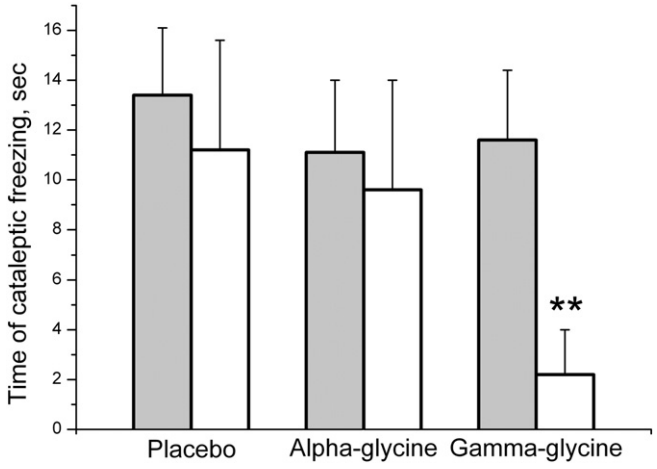

Fig. 3. Effect of glycine treatment on cataleptic behavior in GC rats. Data presented as mean ± SEM. Gray columns — before treatment, white columns — after treatment. ** — $P<0.01$ — before γ-glycine vs. after γ-glycine (t-test for dependent samples).

Catalepsy was first assessed one day after the placement of the rats into individual cages. A day later, the rats began to receive glycine or placebo. Catalepsy was re-assessed on day 15 of treatment. Tests were presented to the same rats as follows. The open-field, day 17; the elevated plus-maze, day 19; and the light–dark box, day 21 of treatment.

The rats from all groups (control and both experimental) were tested in one day. The animals were tested in successive blocks, each block contained one rat from each experimental and control group.

2.4. Catalepsy

Catalepsy was assessed in accordance with the technique described previously (Barykina et al., 1983): the experimentalist put a stick under the forepaws of the animal sitting in a corner of the home cage tail to the wall, began to slowly move the stick upwards thus lifting the upper part of the animal's body until its back was pressed against the cage wall and recorded the time over which the immobile vertical posture so imposed was maintained after the withdrawal of the stick.

2.5. Behavioral tests

We chose to use the open-field, elevated plus-maze, and light–dark box tests. All the behavioral tests started at 14:00. The animal behavior was recorded using a video camera. The observer was in a neighboring room during the test. The videotapes were scored by an observer blind to treatment using an original computer program (Pliusnina et al., 2003). All the devices for behavior testing were cleaned after each trial.

2.6. Open-field test

The open-field device was a 1.0 × 1.0 m plastic platform divided into 10 × 10 cm drawn squares. The 40 × 40 cm area around a wooden cube (7 × 7 × 7 cm) in the center of the platform was regarded as the center of the open field. The platform was bordered by a 40-cm high transparent acrylic plastic wall and illuminated by a 100 W incandescent lamp placed at a height of 100 cm above the platform. The commonly accepted open-field variables — locomotion (scored as the number of squares crossed), the number of rearing events, the total time spent rearing, the number of grooming episodes, the overall time spent grooming, and the number of fecal boluses — were recorded for 5 min (Archer, 1973; Hall, 1934). Additionally, we recorded the total freezing time: when a rat was completely immobile with eyes still open.

2.7. Elevated plus-maze test

The elevated plus-maze had two open arms, 45 × 10 cm, and two closed arms, 45 × 10 × 30 cm. The arms extended from a 10 × 10 cm center platform. The maze was made of opaque Plexiglas. Apparatus was elevated to a height of 60 cm above the floor and was illuminated by a 100 W incandescent lamp placed 100 cm above the center platform. The rats were placed in the center of the maze facing one of the open arms, and their behavior was monitored for 5 min. The following variables were recorded in the elevated plus-maze: the number of open-arm, closed-arm, and total arm entries; the number of closed-arm returns (exiting a closed arm with only two paws and returning to the same arm); the time spent in the various sections of the maze; and the number of stretch–attend postures (SAP, rats stretch forward and retract to the original position without actually locomotion). An event was registered as an arm entry when a rat had its four limbs in an arm at one time. An event was registered as an arm entry when a rat had its four limbs in an arm at a time (Rodgers and Cole, 1994).

2.8. Light–dark box test

The light–dark box (Crawley and Goodwin, 1981) had two compartments of the same size (40 × 40 × 40 cm) separated by an opaque partition with a round hole 8 cm in diameter. The light

Table 1
Results of the open-field test.

Behaviors	M ± SEM			PC1 46.6%	PC2 14.2%
	Placebo	α-Glycine	γ-Glycine		
Latency of locomotion, s	35.0 ± 19.8	18.7 ± 6.4	11.2 ± 2.6	−0.46	0.00
Time of freezing, s	37.6 ± 21.9	14.0 ± 5.0	6.3 ± 2.2	**−0.67**	**0.63**
(Squares for the 1st minute, n)/(total squares, n), %	0.15 ± 0.04	0.18 ± 0.04	0.1 ± 0.02	0.15	**0.78**
Total peripheral locomotion, square number	172.5 ± 26.6	193.9 ± 17.6	187.6 ± 13.2	**0.80**	−0.20
(Central squares, n)/(total squares, n), %	1.7 ± 0.6	3.8 ± 0.9	3.9 ± 0.9	**0.67**	0.09
Episodes of rearing on periphery, n	14.3 ± 2.4	19.3 ± 3.5	22.9 ± 1.6	**0.94**	−0.09
Time of rearing on periphery, s	28.6 ± 5.9	39.4 ± 8.1	46.4 ± 4.2	**0.84**	−0.13
Latency of rearing on periphery, s	81.0 ± 31.6	40.9 ± 10.4	31.3 ± 4.7	**−0.74**	0.44
Episodes of rearing in central squares, n	0.1 ± 0.1	0.7 ± 0.2	0.4 ± 0.2	**0.78**	0.49
Time of rearing in central area, s	0.3 ± 0.3	3.2 ± 1.1	1.9 ± 0.9	**0.66**	0.44
Latency of rearing in central area, s	291.6 ± 10.4	241.1 ± 28.3	249.0 ± 22.3	**−0.67**	−0.53
Episodes of central + peripheral rearing, n	14.4 ± 2.4	20.0 ± 3.6	23.3 ± 1.8	**0.95**	−0.05
Time of central + peripheral rearing, s	28.9 ± 5.9	42.6 ± 8.7	48.3 ± 4.7	**0.88**	−0.06
Episodes of grooming, n	2.1 ± 0.5	2.4 ± 0.5	1.8 ± 0.6	0.47	0.01
Time of grooming, s	5.1 ± 1.7	15.5 ± 4.9	7.2 ± 2.1	0.38	0.16
Boluses, n	2.6 ± 0.7	2.8 ± 0.6	1.9 ± 0.5	−0.13	0.50

Means ± SEM of behavioral measures and loadings on the first two principal components by PCA of behaviors. Loadings higher than 0.6 are in bold.

compartment, made of white Plexiglas, was brightly illuminated by a 100 W incandescent lamp placed 100 cm above the floor of the test box. The dark compartment, made of black Plexiglas, was covered with a non-transparent lid. The animals were placed in the center of the dark compartment, and their activity in the light compartment was monitored for 5 min. The behavioral variables recorded with the light–dark box were the protrusion of the muzzle (to the ear line) or the head and neck into the light compartment and the assumption of stretch–attend postures with the hind paws still in the dark compartment. No episodes of full rat emergence from the enclosed area into the open area were observed in the current experiments.

2.9. Statistics

Data are presented as the means ± standard error of the mean (SEM). The t-test for dependent samples was used to compare the cataleptic behaviors before and after treatment with glycine. Principal component analysis (PCA) was used to analyze the data obtained in the open-field, plus-maze, and light–dark box tests. Based on the Kaiser–Guttman criterion, principal components (PC) with eigenvalues higher than 10% were retained for interpretation and were analyzed by one-way ANOVA and Fisher LSD post-hoc tests. Any confidence level below 0.05 was considered statistically significant. The results were statistically analyzed using Statistica 6.0.

3. Results

3.1. Test for catalepsy

A comparison of pre- with post-treatment scores of catalepsy (Fig. 3) demonstrated that the α-glycine-treated group was unaffected, while the γ-glycine-treated rats revealed a significant reduction in time of catalepsy: from 11.6 ± 2.8 to 2.2 ± 1.8 s ($P = 0.008$).

3.2. Open-field test

Results of PCA of 16 measures in the open-field test (OF) are summarized in Table 1. About 61% of the total variation in the open-field behavior was explained by the PC1 and PC2. PC1 had high positive loadings for rearings, total locomotion, and percentage of squares entered in the center. PC1 also had high negative loadings for freezing and latency of rearing. The influence of the glycine treatment on the behavioral pattern of PC1 is statistically significant: $F[2, 25] = 3.74$, $p = 0.038$ (Fig. 4(a)). The mean scores of PC1 in both glycine treated groups are positive. Post-hoc comparisons showed significant differences between the α-glycine and control groups ($P = 0.038$) and between the γ-glycine and control groups ($P = 0.02$). PC2 had a high positive loading for freezing and for locomotion during the first minute of the test. No difference was observed between the groups by PC2.

3.3. Elevated plus-maze test

Analyses of 13 behavioral measures obtained in the elevated plus-maze (EPM) demonstrated that 69.3% of the behavioral variability is explained by PC1 and PC2 (Table 2). PC1 had high positive loading for the number of stretch–attend postures and total arm entries. Latencies to the stretch–attend postures and to the entrance to the open arm gave a negative loading to PC1. No difference was observed between the groups by PC1. The most significant PC2 positive loading was made by the time spent in the closed arms, and the PC2 negative loading was made by the percent of entries and time spent in the open arms. The behavioral pattern of PC2 was changed significantly in the group receiving γ-glycine: $F[2, 27] = 4.15$, $p = 0.027$ (Fig. 4(b)). Post-hoc comparisons revealed significant differences between γ-glycine and both the control ($P = 0.013$) and α-glycine ($P = 0.028$) groups.

3.4. Light–dark box test

Ten behavioral traits were evaluated in the light–dark box. The two first principal components are responsible for 72.9% of the total behavioral variability (Table 3). PC1 was positively loaded by all the behaviors caused by the attempts of the rats to exit the dark

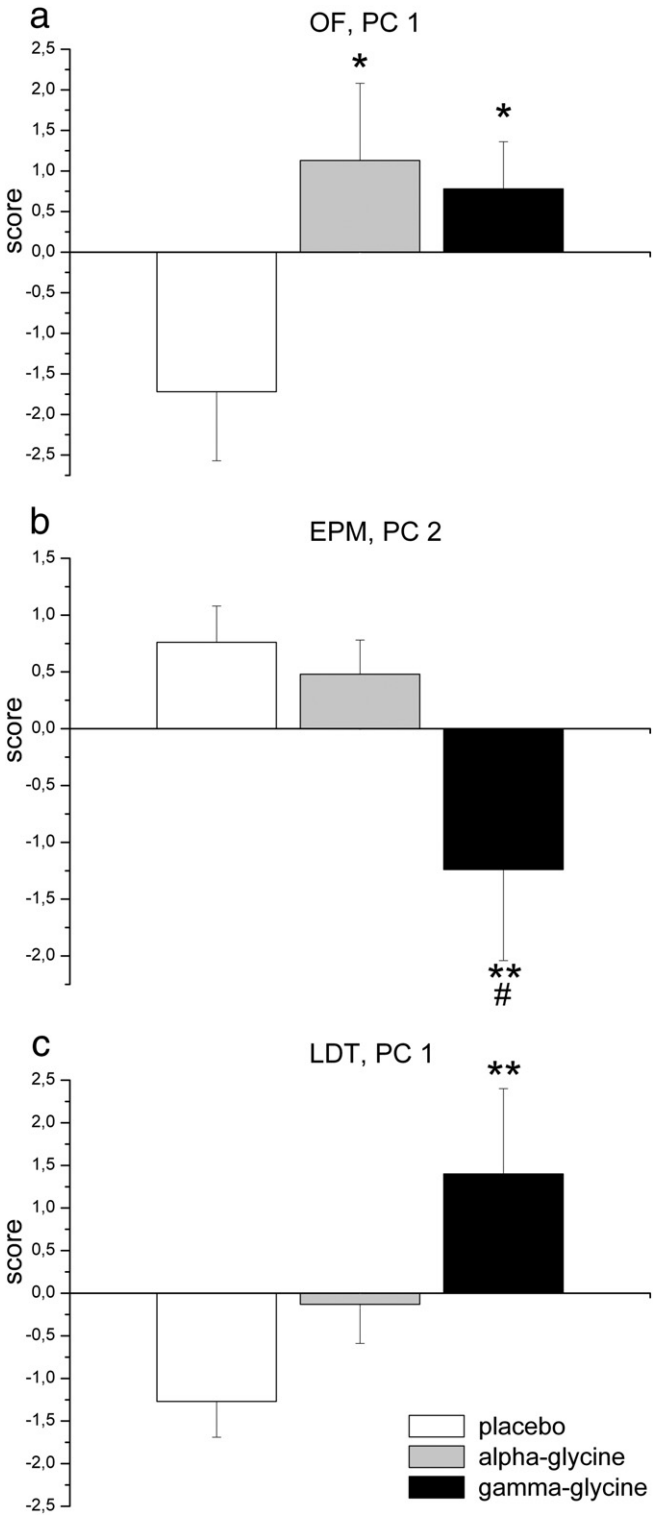

Fig. 4. Mean PC scores of glycine-treated and control groups in behavioral tests. OF — open-field test; EPM — elevated plus-maze test; LDT — light–dark box test. Data presented as mean ± SEM. (a) PC1 of the open-field test. (b) PC2 of the elevated plus-maze test. (c) PC1 of the light–dark box test. * — $P<0.04$, ** — $P<0.013$ — α-glycine, γ-glycine vs. placebo; # _ $P<0.03$ — γ-glycine vs. α-glycine, (Fisher LSD post-hoc test).

Table 2
Results of the elevated plus-maze.

Behaviors	M ± SEM			PC1 42.9%	PC2 26.4%
	Placebo	α-Glycine	γ-Glycine		
Stretch–attend postures, n	4.0 ± 1.2	2.5 ± 0.6	3.8 ± 0.9	**0.88**	0.28
Stretch–attend postures, s	28.3 ± 6.5	15.7 ± 5.0	20.5 ± 6.2	**0.74**	0.38
Latency of stretch–attend posture, s	96.0 ± 31.2	114.4 ± 38.4	101.5 ± 34.6	**−0.75**	−0.32
Closed-arm returns, n	2.0 ± 0.6	1.2 ± 0.4	1.1 ± 0.3	**0.60**	0.32
Closed-arm entries, n	2.8 ± 0.7	2.2 ± 0.4	3.3 ± 0.8	**0.83**	0.21
Open-arm entries, n	1.7 ± 0.6	1.3 ± 0.4	2.4 ± 0.4	**0.84**	−0.26
Total arm entries, n	4.5 ± 1.2	3.5 ± 0.8	5.7 ± 1.0	**0.91**	0.01
Time in center, s	47.1 ± 8.8	29.5 ± 8.9	63.8 ± 18.6	**0.70**	−0.08
Latency of entrance to open arm, s	139.1 ± 44.8	125.4 ± 41.1	32.1 ± 17.4	**−0.66**	0.52
(Open-arm entries, n)/(total entries, n), %	30.1 ± 7.5	27.5 ± 6.7	53.6 ± 9.3	0.27	**−0.87**
Time in open arm, s	29.4 ± 9.9	31.4 ± 11.9	98.4 ± 34.4	−0.01	**−0.92**
Time in closed arm, s	221.9 ± 17.5	237.9 ± 16.1	136.6 ± 30.9	−0.35	**0.87**
Boluses, n	0.9 ± 0.4	1.2 ± 0.3	1.7 ± 0.7	−0.02	−0.50

Means ± SEM of behavioral measures and loadings on the first two principal components by PCA of behaviors. Loadings higher than 0.6 are in bold.

Table 3
Results of the light–dark box.

Behaviors	M ± SEM			PC1 58.3%	PC2 14.6%
	Placebo	α-Glycine	γ-Glycine		
Muzzle protrusion from dark to light box, n	1.8 ± 0.6	2.8 ± 0.6	3.6 ± 1.1	**0.89**	−0.26
Muzzle protrusion from dark to light box, s	4.1 ± 1.8	7.0 ± 1.7	7.8 ± 2.7	**0.78**	−0.32
Latency of muzzle protrusion, s	181.3 ± 36.2	76.9 ± 26.9	100.3 ± 34.6	**−0.66**	0.45
Head protrusion from dark to light box, n	0.6 ± 0.3	1.4 ± 0.5	2.5 ± 0.7	**0.93**	−0.04
Head protrusion from dark to light box, s	1.0 ± 0.5	3.3 ± 1.0	5.8 ± 1.8	**0.87**	−0.19
Latency of head protrusion, s	226.7 ± 32.5	213.5 ± 23.3	128.1 ± 39.4	**−0.80**	0.08
Stretch–attend postures, n	0 ± 0	0.3 ± 0.2	1.2 ± 0.7	**0.78**	0.51
Stretch–attend postures, s	0 ± 0	0.7 ± 0.5	3.8 ± 1.9	**0.77**	0.46
Latency of stretch–attend posture, s	301 ± 0	289 ± 8.6	214.8 ± 40.9	**−0.72**	−0.50
Boluses, n	3.7 ± 0.8	2.9 ± 0.7	3.3 ± 0.6	−0.13	0.57

Means ± SEM of behavioral measures and loadings on the first two principal components by PCA of behaviors. Loadings higher than 0.6 are in bold.

compartment. The experimental groups are significantly different along this PC1 dimension: $F[2, 27] = 3.65$, $P = 0.039$ (Fig. 4(c)). Post-hoc analysis revealed a significant difference of the γ-glycine group from the control group ($P = 0.012$). The γ-glycine-treated rats demonstrated more frequent and intensive attempts to escape the dark compartment of the light–dark box. The PC2 of this test had the maximal positive loading of the defecation score. This dimension failed to distinguish among the three groups of rats.

4. Discussion

The applied analysis of the principal components gave us an opportunity to evaluate the influences of glycine treatment on the underlying motivational structure of the behaviors. In the open-field test, PC1 may be labeled as "exploration". GC rats are characterized by a decrease in these behaviors in the open-field test (Barykina et al., 1983; Petrova, 1990). Therefore the effect of both forms of glycine may be interpreted as anxiolytic (Bouwknecht and Paylor, 2008). Two open-field behaviors, freezing and first-minute locomotion, made a maximal positive loading to PC2, allowing us to define this component as "fearfulness" (Markel et al., 1989).

PCA confirmed the independence of the indices of total activity, which load PC1, and anxiety in the elevated plus-maze (Fernandes and File, 1996; File, 2001). PC1 also had a high positive loading for the stretch–attend posture and could be designated as "general activity and risk-assessment behavior". The increased time spent in the closed arms and the low episodes of entrance into the open arms correspond to enhanced emotional reactivity and anxiety (Rodgers and Cole, 1994). Namely, these patterns made a substantial loading to PC2. The γ-glycine treated rats had a negative and significantly different from the two groups PC2 score. We can conclude that the rats from the γ-glycine group are less anxious than the rats from the control and α-glycine groups in the plus-maze test.

PC1 in the light–dark box test likely reflected exploratory activity. We may thus conclude that rats in both glycine groups are less anxious and have a higher tendency to explore the light compartment of the box than the control rats. The biological interpretation of PC2 in the light–dark box test is not obvious. The most loading to PC2 in this test was by the defecation score. We may consider this dimension as "emotionality" (Broadhurst, 1957; Hall, 1934); however, others have questioned the validity of defecation as index of emotionality of rats (Archer, 1973). No differences were found between the rat groups in this dimension.

The simultaneous reduction of catalepsy and anxiety in the γ-glycine group is not unexpected, because expression of the passive–defensive reaction and anxiety in the elevated plus-maze is potentiated by fear (Kolpakov et al., 1996; Korte and De Boer, 2003). The mechanisms that mediate these effects are probably related to the ability of glycine to activate the GABA and glutamatergic NMDA receptors (Smith, 1996). Both systems are associated with reactions of fear and anxiety (Davis et al., 1994; Cortese and Phan, 2005; Walker et al., 2002).

The rationale for the use of glycine in the treatment of patients with neurological diseases and schizophrenia has been suggested in many works (Javitt et al., 1994). Glycine acts as a coagonist for glutamate at the NMDA receptor complex (Laube et al., 1997). Clinical trials in which NMDA receptor activity was enhanced by agents acting on the glycine modulatory site have demonstrated decreases in negative symptoms in patients with schizophrenia and improvements in cognitive function (Hons et al., 2010). On the other hand, NMDA

receptor hypofunction has been shown to be critically involved in the etiology and pathophysiology of negative symptoms (Goff and Coyle, 2001; Heresco-Levy et al., 1999; Marek et al., 2010). Stimulation of the glycine modulatory sites on the NMDA receptors either directly with D-serine or by blocking glycine transporter-1 enhances social memory and may be an effective approach for the treatment of the cognitive dysfunction (Shimazaki et al., 2010). Thus, improvement in the cognitive ability and a decrease in the negative symptoms by the drugs modulating glutamatergic neurotransmission, including glycine, can be related to the drug–NDMA-receptor interaction (Coyle and Tsai, 2004; Lipina et al., 2005).

We may conclude that both forms of glycine have beneficial effects on the behavior of GC rats, and that the effect of γ-glycine is more pronounced in the elevated plus-maze and light–dark box tests, especially in reducing the propensity to cataleptic responses. The difference in the effects of α- and γ-glycine reported here is very remarkable. Differences in bioavailability of polymorphs of the same compound are usually related to differences in solubility or dissolution kinetics (Bernstein, 2002; Brittain, 1999; Hilfiker, 2006; Shakhtshneider and Boldyrev, 1999). Both α- and γ-glycine, however, are quite soluble (Yang et al., 2008), thereby discounting this simple explanation. An alternative explanation might be that crystals of glycine may not dissolve as individual molecules, but as clusters of molecules, "remembering" the way how the molecules were linked together in the crystal. The degree of interaction between glycine and the receptors' active site may thus depend on the degree to which hydrogen bonds are broken within clusters or on the ability of forming supramolecular complexes between receptors and clusters of glycine molecules, but not with single molecules. Both characteristics can be expected to differ between α- and γ-glycine. Some indirect data support this hypothesis. Solutions of glycine were noticed "to have memory", i.e. to differ in structure and properties, at least during some measurable time after preparation from different polymorphs. In particular, the outcome of the crystallization of a polymorph has been shown to depend on the original polymorph from which this solution has been initially prepared, unless the solution has been aged for several days or longer (Boldyreva et al., 2003a; Boldyreva, 2007). Studies of the dissolution of single crystals of the α-polymorph in water with atomic-force microscopy, phase-measurement interferometric microscopy, and grazing-incidence X-ray diffraction have shown that the "elementary dissolution step" includes two individual layers of glycine zwitter-ions, i.e. the crystal is dissolved not "molecule by molecule" but by preserving centrosymmetric glycine dimers (Carter et al., 1994; Gidalevitz et al., 1997). The presence of glycine dimers in an aqueous solution prepared from the α-polymorph has been confirmed by small-angle scattering experiments (Chattopadhyay et al., 2005; Erdimir et al., 2007; Hughes et al., 2007).

In summary, we conclude that glycine produced a significant improvement in the behavior of cataleptic GC rats. The beneficial effect of glycine on the behavior of these rats is similar to that observed in schizophrenic patients. The novel results provide support for our earlier idea that the GC strain of rats is an advantageous model of schizophrenia-like behavioral disorders. The most important result of the current study is that γ-glycine had higher biological activity than α-glycine in ameliorating the behavioral disorders in the GC strain. The origin of this newly observed phenomenon will require further study and may be related to differences in the supramolecular complexes formed during the interaction of the two polymorphs with biological liquids and the drug receptors. This phenomenon offers a new opportunity for developing much more active therapeutic agents for treating behavioral pathology.

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