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The kynurenine 3-hydroxylase inhibitor Ro 61-8048 improves dystonia in a genetic model of paroxysmal dyskinesia

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Abstract

The effects of the novel kynurenine 3-hydroxylase inhibitor 3,4-dimethoxy-*N*-[4-(3-nitrophenyl)thiazol-2-yl]benzenesulfonamide (Ro 61-8048) on severity of dystonia were examined in dt^{sz} mutant hamsters, an animal model of paroxysmal dystonia, in which stress precipitates dystonic episodes. Ro 61-8048 (50, 100 and 150 mg/kg i.p.) significantly reduced the severity of dystonia in dt^{sz} hamsters without leading to marked central side effects. Determinations of kynurenic acid concentrations in brain homogenates demonstrated that Ro 61-8048 (100 mg/kg i.p.) provoked a two- to threefold increase of the endogeneous broad spectrum glutamate receptor antagonist kynurenic acid in the striatum, cerebellum and brainstem of mutant hamsters. The antidystonic efficacy of Ro 61-8048 at well-tolerated doses suggests that kynurenine 3-hydroxylase inhibitors should be considered as new therapeutic candidates for the treatment of dyskinesias.

Keywords: Choreoathetosis; Dyskinesia; Glutamate; Kynurenic acid; Kynurenine hydroxylase; Movement disorder

1. Introduction

Kynurenic and quinolinic acids are two metabolites of the kynurenine pathway for the metabolism of L-tryptophan, with opposite actions on glutamate receptors (Schwarcz and Pellicciari, 2002; Stone, 2001a,b; Wu et al., 2000). Kynurenic acid is an antagonist of all ionotropic glutamate receptors with preferential affinity for the glycine site of the *N*-methyl-D-aspartate (NMDA) receptor (Schwarcz and Pellicciari, 2002). Furthermore, kynurenic acid can reduce the glutamate release (Carpenedo et al., 1999). Changes of the kynurenine pathway were found in neurodegenerative diseases, including movement disorders such as Parkinson's disease and Huntington's disease (Stone, 2001b). In contrast to these neurodegenerative movement disorders, the role of abnormalities of the glutamatergic system and of kynurenines has not been examined in dystonias. Dystonias, characterized by sustained muscle contractions frequently causing twisting and repetitive movements or abnormal postures, seem to be related to basal ganglia dysfunctions (Vitek and Giroux, 2000). The neurochemical basis is probably heterogeneous in different types of dystonia. The lack of knowledge about the pathophysiology hampers the development of rational drug therapies.

As indicated by previous examinations in the dt^{sz} mutant hamster, one of the few well-defined animal models of dystonia, the glutamatergic system deserves attention (Richter and Löscher, 1998, 2002). The dt^{sz} mutant hamster shows the characteristics of primary paroxysmal non-kinesigenic dyskinesia (in brief: paroxysmal dystonia) in humans (Nardocci et al., 2002; Richter and Löscher, 2002). In this type of dystonia, episodes of generalized dystonic and choreoathetotic movements can be provoked by stress and last up to several hours. Under basal condition, i.e., in the absence of dystonic attacks, there were no gross changes of excitatory amino acid levels in tissue homogenates and glutamate receptor binding within regions of the motor system in dt^{sz} hamsters (Löscher and Hörstermann, 1992; Nobrega et al., 1997, 2002). However, altered NMDA and α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) receptor binding during the expression of dystonia suggested that glutamatergic overactivity contributes to the manifestation of dystonic episodes (Nobrega et al., 1997, 2002). In view of antidystonic effects of different synthetic glutamate receptor antagonists in

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mutant hamsters, ontogenetically enhanced kynurenic acid levels in dystonic brains have been interpreted as a compensatory mechanism in response to glutamatergic overactivity (Richter and Löscher, 1998; Richter et al., 1996). However, the relevance of these changes for the occurrence of dystonia remained unclear.

The most effective way to increase simultaneously the brain concentrations of kynurenic acid and decrease the amount of 3-hydroxykynurenine and quinolinic acid consists in the treatment with selective inhibitors of the kynurenic acid degrading enzyme kynurenine 3-hydroxylase (Chiarugi and Moroni, 1999; Schwarcz and Pellicciari, 2002; Stone, 2001a). The novel compound 3,4-dimethoxy-*N*-[4-(3-nitrophenyl)thiazol-2-yl]benzenesulfonamide (Ro 61-8048) exerts high activity as an inhibitor of kynurenine 3-hydroxylase and has been shown to provoke a significant increase of extracellular kynurenic acid concentrations (Cozzi et al., 1999; Röver et al., 1997; Urenjak and Obrenovitch, 2000).

The present data have been published previously in abstract form (Hamann and Richter, 2002).

2. Methods

2.1. Animals

The present experiments were carried out in groups of male and female dt^{sz} mutant Syrian golden hamsters. The animals were obtained by selective breeding as described in detail elsewhere (Fredow and Löscher, 1991). All hamsters were born and kept under the same controlled and constant environmental conditions. The experiments were done in compliance with the German Animal Welfare Act.

2.2. Induction of dystonic attacks and severity-score of dystonia

Motor impairments in dt^{sz} hamsters show several features in common with human primary paroxysmal non-kinesigenic dystonia (paroxysmal dystonic choreoathetosis), characterized by long-lasting dystonic attacks (Nardocci et al., 2002; Richter and Löscher, 1998). In mutant hamsters, dystonic attacks can be reproducibly induced by a triple stimulation technique, i.e., stressful stimuli consisting of (1) taking the animal from its home cage and placing it on a balance, (2) injection of saline/vehicle (or of drugs), and (3) placement of the animal in a new plastic cage. Thereafter, dt^{sz} hamsters develop a sequence of abnormal movements and postures. The severity of dystonia can be rated by following score system (Löscher et al., 1989; Richter and Löscher, 1998): stage 1, flat body posture; stage 2, facial contortions, rearing with forelimbs crossing, disturbed gait with hyperextended forepaws; stage 3, hyperextended hindlimbs so that the animals appear to walk on tiptoes; stage 4, twisting movements and loss of balance; stage 5, hindlimbs hyperextended caudally; stage 6, immobilisation in a twisted, hunched posture with hind- and forelimbs tonically extended forward. The individual maximum stage of dystonia is usually reached within 3 h after the hamsters were placed in the new cage. Thereafter, the hamsters recover within 2–5 h.

The dystonic syndrome in dt^{sz} mutants shows an age-dependent time-course (e.g., Richter and Löscher, 1998). The severity of dystonia reaches a maximum at an age of about 32–42 days. Then, the severity slowly declines until complete remission occurs at an age of about 10 weeks. In the present study, all animals were examined for the presence of dystonia after weaning at the age of 21 days by the triple stimulation procedure three times per week until the animals exhibited constant individual severity scores and latencies to onset of unequivocal dystonic symptoms (stage 2). The present drug experiments were done during the life-period of maximum expression of dystonia. Not all hamsters reach stage 6, but the individual maximum severity and the latency to onset is usually reproducible during this period (Richter and Löscher, 1998). To obtain reproducible latencies and avoid onset of dystonia prior or during the triple stimulation technique, it was important to keep in time from taking the animals out of their home cage to placing them in a new cage (duration: 25–35 s). The animals did not exhibit dystonic symptoms before injections of drug or vehicle.

2.3. Drug treatments

The effects of Ro 61-8048 (50, 100 and 150 mg/kg i.p.) on the severity of dystonia were examined in groups of 6–12 dystonic hamsters. Each group was used for one dose. Dystonic attacks were induced by the procedure of triple stimulation, as described above. Since the individual maximum stage of dystonia (score rating system see above) is usually reached within 3 h, the hamsters were observed for 3 h after triple stimulation. For drug testing, a control trial was undertaken with the triple stimulation technique, injecting the vehicle i.p. and the latencies and severity of the dystonic attacks were noted after placing the animals in the new cage (pre-drug control). Two days later, the drug was administered in the same group of animals and the latency and severity were noted. Furthermore, animals were observed for central adverse effects, e.g., locomotor activity, ataxia and stereotypies. As described for pre-drug controls, a control trial with vehicle was done 2 days after drug treatment (post-drug control). Hamsters that differed in the maximum severity of dystonia reached during the 3-h observation period in the pre-drug and post-drug control trials by more than two stages were omitted from the drug evaluation. All control and drug trials were done at the same time of the day between 9:00 and 12:00 a.m.

The examiner rating the severity of dystonia was blind to the treatment condition of the animals. The side effects were observed by a second examiner. As in previous studies, the adverse effects such as the locomotor activity

were determined by a score system (e.g., Richter and Hamann, 2001).

2.4. Drugs

The kynurenine 3-hydroxylase inhibitor Ro 61-8048 (3,4-dimethoxy-*N*-[4-(3-nitrophenyl)thiazol-2-yl]benzenesulfonamide), kindly provided by Hoffmann-La Roche (Basel, Switzerland), was freshly suspended in 0.3% Tween 80 prior the experiments. The injection volume for drug and vehicle administrations was 5 ml/kg.

2.5. Determinations of kynurenic acid

For determinations of kynurenic acid, two groups of eight male and female dt^{sz} were used. One group of dt^{sz} mutants received Ro 61-8048 (100 mg/kg i.p.) and one group of mutant hamsters was treated with vehicle (0.3% Tween 80, 5 ml/kg) 90 min prior decapitation. In mutant hamsters treated with Ro 61-8048, the severity of dystonia was determined prior decapitation and the severity was compared with the severity reached during the pre-drug vehicle control.

The brains were rapidly removed and dissected into striatum, cerebellum and brainstem. As previously described (Richter et al., 1996), the regions were weighed and homogenized in 1.2 ml of 0.1 N HCl. The homogenates were centrifuged at 18,000 rpm for 15 min at 4 °C. Then 1 ml of the supernatant was applied to a Dowex-50 W cation-exchange resin in a Pasteur pipette after pre-washing with 1 ml of 0.1 N HCl. The column was washed again with 1 ml of 0.1 N HCl and 1 ml of water, and the fraction containing kynurenic acid was eluted with 3 ml of water. The eluates were frozen, lyophilized and then stored at −80 °C until analysis. Prior to measurements, the samples were re-suspended in 150 μl of water. Kynurenic acid was measured by high-performance liquid chromatography (HPLC) according to methods previously described (e.g., Richter et al., 1996; Swartz et al., 1990). In brief, 100 μl of the probe was applied to a 3-μm Spherisorb ODS HPLC column (125 × 4-mm internal diameter; Bischoff Analysentechnik, Leonberg, Germany). Two mobile phases (A and B) were simultaneously pumped through the column by two pumps at a flow rate of 0.4 ml/min and a relation of 60% phase A (0.5 M zinc acetate) and 40% phase B (0.1 M sodium acetate/40% acetonitrile, pH 6.3). Kynurenic acid was detected by a fluorescence detector (4.5-min retention time) using excitation at 344 nm and emission at 389 nm (sensitivity limit: 170 fmol).

2.6. Statistics

The significance of differences (severity of dystonia, latencies to onset of dystonia) between control trials (pre-

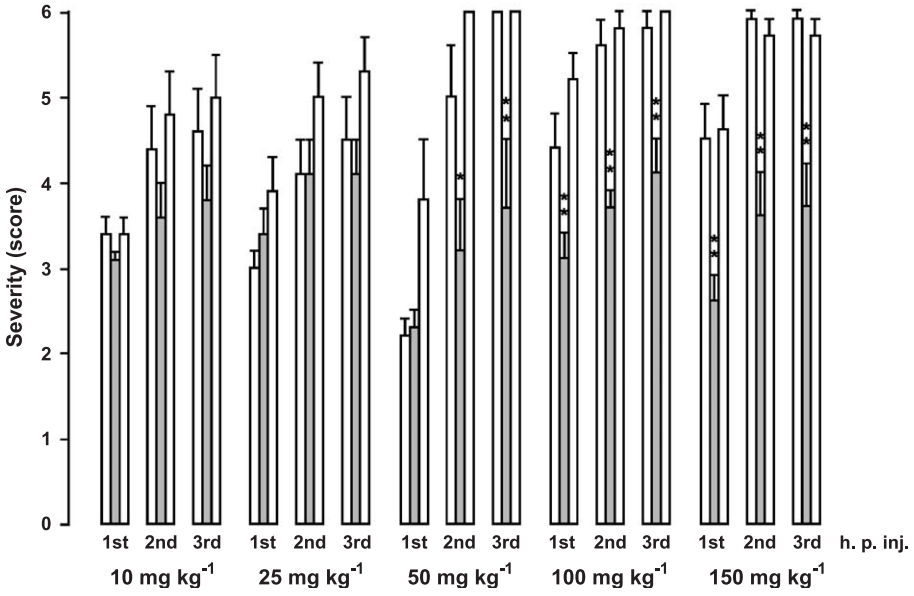

Fig. 1. Effects of kynurenine 3-hydroxylase inhibitor Ro 61-8048 (50, 100 and 150 mg/kg i.p.) on severity of dystonia in mutant hamsters. The white bars in each set of three bars indicate the control values obtained 2 days before (pre-drug control) drug administration (first white bar) and 2 days after (post-drug control) drug administration (second white bar). The grey bar refers to the day of drug administration in the same animal groups. The individual maximum severity of dystonia is usually reached within 3 h after induction of dystonia by triple stimulation including the injection of drugs or vehicle. The figure shows the average of the maximum individual severity scores of dystonia reached within the 1st, 2nd and 3rd h post-injection (p. inj.) of vehicle or Ro 61-8048, reflecting the progression of dystonia in dt^{sz} hamsters after treatment with the active compound and during control recordings. Asterisks indicate significant improvements of dystonia in comparison to the pre- and post-drug control (*$P < 0.05$, **$P < 0.01$). Data are shown as means + S.E. of 6–12 dystonic hamsters. Absence of S.E. bars indicates that all hamsters had reached the same severity.

and post-drug) and drug trial in the same group of animals was calculated by the Friedman test and, if there was found a significant difference (at least $P<0.05$), the Wilcoxon signed rank test for paired replicates was used post hoc to determine which pairs differed. The significance of differences in kynurenic acid concentrations between different groups was evaluated by ANOVA and, since there was found a significant difference (at least $P<0.05$), the Student's *t*-test for grouped data was used to analyse which groups differed.

3. Results

Ro 61-8048 significantly reduced the individual maximum severity of dystonia reached at the end of the observation period of 3 h at doses of 50, 100 and 150 mg/kg i.p. (Fig. 1). Already during the first hour, after the induction of a dystonic attack, 100 and 150 mg/kg significantly decreased the severity, indicating a fast onset of action. A delayed onset of dystonic attacks was observed after treatment with 150 mg/kg but not after administration of 50 and 100 mg/kg (Table 1). At lower doses of 10 and 25 mg/kg, Ro 61-8048 failed to exert any antidystonic effects (Table 1, Fig. 1). Ro 61-8048 caused a moderate sedation and hypolocomotion 5 to 70 min after administration of 100 and 150 mg/kg, while no central adverse effects were observable at a dose of 50 mg/kg or lower doses.

Fig. 2 shows the kynurenic acid levels in tissue homogenates 90 min after treatment with Ro 61-8048 (100 mg/kg) or after administration of the vehicle. At the effective dose of 100 mg, the kynurenine 3-hydroxylase inhibitor significantly increased the kynurenic acid levels in the striatum, cerebellum and brainstem of mutant hamsters (Fig. 2). The kynurenic acid concentration was two- to threefold higher in these brain regions of hamsters treated with the kynurenine 3-hydroxylase inhibitor than in animals treated with 0.3% Tween 80, i.e., the vehicle. Prior decapitation for the determinations of kynurenic acid levels, i.e., during the first 90 min after treatment with 100 mg/kg Ro 61-8048, the severity of dystonia was significantly reduced in mutant hamsters in comparison to pre-drug vehicle controls undertaken 2 days before drug treatment (not illustrated). The data confirm the antidystonic effect of Ro 61-8048 at a dose that increases kynurenic acid levels (Fig. 2).

Table 1
Effects of intraperitoneal injections of Ro 61-8048 on latency to onset of dystonia in dt^{sz} mutant hamsters

Dose (mg/kg i.p.)	Latency (min)			(*n*)
	Pre-drug	Drug	Post-drug	
10.0	8.6 ± 1.4	5.8 ± 0.8	11.1 ± 1.6	8
25.0	6.6 ± 0.8	10.1 ± 2.3	6.9 ± 1.0	8
50.0	9.7 ± 2.0	5.7 ± 1.3	7.0 ± 0.6	6
100.0	5.7 ± 0.5	9.3 ± 2.7	4.9 ± 0.7	9
150.0	7.6 ± 0.6	22.8 ± 3.2[a]	8.8 ± 1.3	12

Latency was determined as the time to the first unequivocal signs of the dystonic attacks (stage 2). Data are shown as means ± S.E. of the number of animals indicated (*n*). Significant differences to pre-drug and post-drug controls are marked by ([a]$P<0.01$).

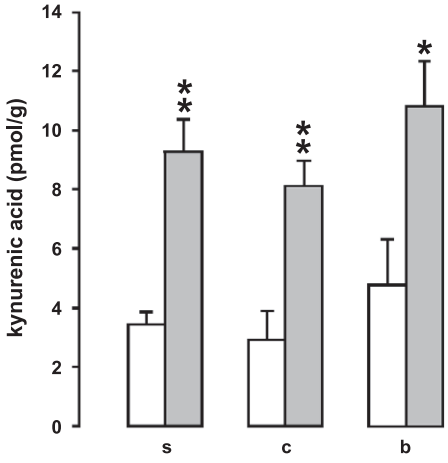

Fig. 2. Kynurenic acid levels in the striatum (s), cerebellum (c) and brainstem (b) in dt^{sz} hamsters after administration of vehicle (open bars) or Ro 61-8048 at a dose of 100 mg/kg i.p. (grey bars). The data (pmol/g of tissue) are shown as means + S.E. Asterisks indicate a significant increase of kynurenic acid levels after treatment with Ro 61-8048 in comparison to vehicle control (*$P<0.05$; **$P<0.01$).

4. Discussion

The present study demonstrates for the first time beneficial effects of a kynurenine 3-hydroxylase inhibitor in a type of dystonia. While NMDA receptor antagonists, such as dizocilpine, caused marked side effects (hyperactivity, ataxia, stereotypies) at antidystonic effective doses in mutant hamsters (Richter et al., 1991), Ro 61-8048 significantly reduced the severity of dystonia at well-tolerated doses.

Treatment with the antidystonic effective dose of 100 mg/kg Ro 61-8048 resulted in a two- to threefold increase of kynurenic acid in different brain regions of mutant hamsters. This result suggests that basal increases of kynurenic acid levels previously found in brains of mutant hamsters at the most sensitive age of dystonia (Richter et al., 1996) do not cause dystonic symptoms, but may represent an (insufficient) attempt to compensate a glutamatergic overactivity. Two- to threefold increases of kynurenic acid in brain homogenates, found after treatment with the antidystonic effective dose of 100 mg/kg Ro 61-8048 in mutant hamsters, do not necessarily mean that extracellular concentrations enhance to a similar amount. However, Urenjak and Obrenovitch (2000) demonstrated by microdialysis a two- to threefold increase of extracellular kynurenic acid levels 90 min after intraperitoneal injections of 100 mg/kg Ro 61-8048 in the striatum of rats.

Interestingly, Urenjak and Obrenovitch (2000) demonstrated that such an increase of kynurenic acid was not associated with any inhibition of NMDA-induced electrophysiological responses. Although only a trend toward reduced NMDA responses was detected in rats treated with 100 mg/kg Ro 61-8048 (Scharfman et al., 2000), even low increases of kynurenic acid concentrations have been reported to exert behavioral effects, e.g., sedation as observed in mutant hamsters after administration of 100 and 150 mg/kg Ro 61-8048, and physiological consequences (Carpenedo et al., 1999). Low micromolar concentrations of kynurenic acid antagonize the glycine site of the NMDA receptor complex, while at higher levels of 0.1 to 1 mM kynurenic acid also inhibits AMPA and kainate receptors (Moroni, 1999). Carpenedo et al. (1999) have shown that striatal administration of kynurencic acid at low concentrations of 30–100 nm reduced the glutamate release in this basal ganglia structure possibly by inhibition of acetylcholine α7 nicotinergic receptors. With regard to recent findings which indicated that a disinhibition within the striatum of mutant hamsters is critically involved in the dystonic syndrome (Bennay et al., 2001; Gernert et al., 2000; Nobrega et al., 2002), an inhibition of the glutamate release in the striatum by increased kynurenic acid levels may be essential for the antidystonic efficacy of Ro 61-8048 in dt^{sz} hamsters.

The antidystonic effects of Ro 61-8048 were comparable to a low-efficacy partial agonist of the glycine modulatory site of the NMDA receptor complex (Löscher and Richter, 1993) and were even more marked than those of well-tolerated doses of selective NMDA receptor or AMPA receptor antagonists in mutant hamsters (Richter et al., 1991, 1993). These previous pharmacological data together with the present results support recent neurochemical findings, which indicated that enhanced glutamatergic activity contributes to the manifestation of dystonic episodes (Nobrega et al., 1997, 2002; Richter et al., 1991, 2000). In view to the findings that elevations of kynurenic acid levels by treatment with 100 mg/kg Ro 61-8048 have no or only moderate effects on NMDA-induced responses (Urenjak and Obrenovitch, 2000; Scharfman et al., 2000), the antidystonic efficacy of Ro 61-8048 may be related to alternative mechanisms. Thus, Carpenedo et al. (2002) suggested that Ro 61-8048 has antiglutamatergic effects that are unrelated to a rise in kynurenic acid. This could at least explain the early onset of beneficial effects of Ro 61-8048 in mutant hamsters, particularly shown at the highest dose of 150 mg/kg which delayed the onset of a dystonic attack.

Further studies should clarify the relationship of the antidystonic efficacy and changes in kynurenic acid levels and if other kynurenine 3-hydroxylase inhibitors also exert antidystonic effects. Since Ro 61-8048 showed significant antidystonic effects at well-tolerated doses, this compound might be an interesting candidate for the treatment of paroxysmal dyskinesias.

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