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Behavioural Response to Pharmacologic Manipulation of Serotonin Receptors in the Genetically Dystonic Hamster

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RICHTER, A. AND W. LÖSCHER. *Behavioural response to pharmacologic manipulation of serotonin receptors in the genetically dystonic hamster.* PHARMACOL BIOCHEM BEHAV **52**(4) 655–665, 1995.—The genetically dystonic (*dt*^{sz}) hamster is an autosomal recessive mutant that shares several features with paroxysmal dystonia, i.e., a subcategory of inherited idiopathic dystonia in humans. Because the serotonin (5-HT) system has been suggested to be involved in dystonia, we examined the functional responsiveness of the 5-HT system in dystonic hamsters by administering various 5-HT agonists and antagonists selective for different receptor subtypes and observing the effects on dystonic attacks as well as the behavioural responses associated with drug administration. Paradoxically, marked prodystonic effects (i.e., increased severity and/or decreased latency of dystonic attacks) were seen with both the selective 5-HT$_{1A}$ receptor agonist 8-hydroxy-2(di-*n*-propylamino)tetralin (8-OH-DPAT) and the selective and "silent" 5-HT$_{1A}$ receptor antagonist, *N*-tert-butyl-3[4-(2-methoxyphenyl)piperazin-1-yl]-2-phenylpropionamide [(+)-WAY-100135], whereas other 5-HT$_{1A}$ receptor antagonists, i.e., methyl 4[4-(4-[1,1,3-trioxo-2H-1,2-benzoiosothiazol-2-yl]butyl)-1-piperazinyl]1-H-indole-2-carboxylate (SDZ 216-525) and N^1-bromoacetyl-N^8-3′-(4-indolyloxy)-2′-hydroxypropyl-(Z)-1,8-diamino-*p*-methane (pindobind-5-HT$_{1A}$) did not alter dystonia to any comparable extent. Because among these 5-HT$_{1A}$ receptor antagonists, (+)-WAY-100135 is the only drug known to be not only silent at postsynaptic but also presynaptic (somatodendritic) 5-HT$_{1A}$ receptors, the marked prodystonic effect of this drug could relate to increased 5-HT release as a result of the blockade of somatodendritic 5-HT$_{1A}$ receptors. The only 5-HT$_{1A}$ receptor antagonist that exerted antidystonic effects in hamsters was pindolol, which, however, could be related to its β-adrenoceptor blocking action. The 5-HT$_{1A}$ receptor partial agonist ipsapirone exerted moderate prodystonic activity. Prodystonic activity was also determined for the mixed 5-HT$_{1A}$/5-HT$_2$ receptor agonist 5-methoxy-*N*,*N*-dimethyltryptamine, although this drug was less potent in this regard than 8-OH-DPAT. The 5-HT$_2$ receptor agonist 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) exerted prodystonic effects in mutant hamsters, which, however, were also seen after the administration of the 5-HT$_2$ receptor antagonist ritanserin. Collectively, the results of this study demonstrate that dystonia in genetically dystonic hamsters can be affected by pharmacologic manipulation of 5-HT receptors. The data may also indicate that dystonia is not a potential clinical application for selective 5-HT$_{1A}$ or 5-HT$_2$ receptor antagonists.

5-Hydroxytryptamine Dystonia Ipsapirone Ritanserin Serotonin syndrome

ABNORMAL serotonergic function has been implicated in several movement disorders such as Parkinson's disease, tardive dyskinesia, Huntington's chorea, myoclonus, and dystonia (10,50). In postmortem studies on patients with idiopathic (primary) dystonia (i.e., a hyperkinetic syndrome with sustained involuntary twisting movements and abnormal postures), increased levels of serotonin (5-HT) and/or its metabolite, 5-hydroxyindoleacetic acid (5-HIAA), were found in several brain regions, including the basal ganglia (23), which are thought to be pathophysiologically involved in idiopathic dystonia (40). Benzodiazepines, which decrease serotonin (5-HT) turnover presumably via facilitation of GABAergic transmission in the raphe nucleus (6,16), are among the few drugs that produce some relief from the symptoms of dystonia in humans (40). In the genetically dystonic (*dt*) rat, a model of idiopathic dystonia, altered behavioural responses to 5-HT receptor agonists were reported, suggesting a developmental abnormality in the 5-HT system (41,56). Indeed, alterations in

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5-HT metabolism were recently determined in the inferior olive of the dystonic rat (26). In another genetic model of dystonia, the "Wriggle Mouse Sagami" (WMS), increased 5-HT metabolism was found in several brain regions, including the basal ganglia, and the 5-HT_2 receptor antagonist ritanserin effectively inhibited the dystonic symptoms in this mutant (24). We recently reported widespread activation of brain 5-HT systems in genetically dystonic hamsters, a model of paroxysmal dystonia (36) (i.e., a subcategory of inherited idiopathic dystonia in humans) (40). However, unexpectedly, the novel "silent" 5-HT_{1A} receptor antagonist *N*-tert-butyl-3[4-(2-methoxyphenyl)piperazin-1-yl]-2-phenylpropionamide [(+)-WAY-100135] aggravated dystonic attacks in mutant hamsters (35) in contradiction of a previous proposal that 5-HT_{1A} receptor antagonists may be of therapeutic benefit in treating the symptoms of dystonia (56). This prompted us to study the effects of pharmacologic manipulation of 5-HT receptors in the dystonic hamster model in more detail. Three different 5-HT_{1A} receptor antagonists were compared: (+)-WAY-100135 (11), methyl 4[4-(4-[1,1,3-trioxo-2H-1,2-benzoiosothiazol-2-yl]butyl)-1-piperazinyl]1-H-indole-2-carboxylate (SDZ 216-525) (51), and N^1-bromoacetyl-N^8-3′-(4-indolyloxy)-2′-hydroxypropyl-(Z)-1,8-diamino-*p*-methane (pindobind-5-HT_{1A}) (29). Furthermore, the β-adrenoceptor antagonist pindolol, which—because of its high affinity for 5-HT_{1A} receptors—is often used as a 5-HT_{1A} receptor antagonist [e.g., (4,5,52,54)], was included in the study. In addition to 5-HT_{1A} receptor antagonists, the partial agonist ipsapirone (17) and 8-hydroxy-2(di-*n*-propylamino)tetralin (8-OH-DPAT), i.e., the prototype agonist at this receptor subtype (53) were evaluated in the hamster model. Another prototype 5-HT receptor agonist, 5-methoxy-*N*,*N*-dimethyltryptamine (5-MeO-DMT), which stimulates both 5-HT_{1A} and 5-HT_2 receptors (19,38,52-54), was also used in the experiments. Finally, the effects of the 5-HT_2 receptor agonist 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) (20) and the 5-HT_2 antagonist ritanserin (28) were studied. Based on our recent study showing increases in 5-HT or 5-HIAA in several brain areas of mutant dystonic hamsters (36), we expected that 5-HT antagonists would decrease, whereas 5-HT agonists would increase the severity of dystonic attacks in these animals.

METHODS

Animals

The mutant dt^{sz} hamsters and nondystonic control hamsters used in the present experiments were obtained by selective breeding as described in detail elsewhere (15). The hamsters were housed in groups of thre to five animals in plastic cages at an ambient temperature of 23–25°C with a light cycle of 13 h (light on at 0600 h), and were fed on Altromin 1320 standard diet (Altromin, Lage, FRG). All experiments were carried out in the morning (0830–1200 h) at controlled temperatures (23–25°C). In all experiments, animal groups consisted of male and female hamsters, because there was no indication of sex-related differences in dystonia or the effect of drugs on dystonia. A total of 295 dystonic hamsters were used for the present experiments.

Drug Testing

Prior to drug experiments, groups of nine to 17 dystonic hamsters were repeatedly challenged by a triple stimulation technique (15) consisting of: a) taking the animal from its home cage and placing it on a balance; b) intraperitoneal (IP) injection of vehicle (usually saline); and c) placement of the animals in a new (clean and empty) plastic cage (one animal per cage). The duration of this triple stimulation (from taking the animal from its home cage to onset of placement in the new cage) was 20–30 s. Latency to dystonic movements was defined as the time from placing the animal in the new cage to onset of the first clear signs of a dystonic attack (usually stage 2; see subsequent description). The triple stimulation technique resulted in shorter and more reproducible latencies to onset of the dystonic attack than each of the three stimulation components alone, indicating a "stimulus summation" phenomenon. In view of this stimulus summation and the fact that weighing and injection are necessary components of drug experiments, it was essential to use these components during control trials as well. To obtain reproducible latencies with the triple stimulation technique and avoid the onset of dystonia during weighing or injection, it was important to keep the time from taking the animals out of their home cage to placing them in the new cage as short and constant as possible. Hamsters that exhibited dystonic movements before placement in the new cage were omitted from the evaluation.

The predrug testing was started after the hamsters were weaned at the age of 21 days, and was repeated at interstimulation intervals of 2–3 days until reproducible latency and severity of dystonic movements were obtained. The maximum severity of dystonia was usually reached at 30 days, after which reproducible latency and severity were recorded for about 10 days. After 40 days of age, the severity of the dystonic movements slowly declined, and the latency to onset of dystonic movements markedly increased. This period (postmax period) after the age (max period) with maximum susceptibility to induction of dystonic attacks can ideally be used to determine the prodystonic effects of drugs (15). Thus, most drugs of the present study were evaluated both in the max and postmax periods in dystonic hamsters. The term "prodystonic" was used in this study to indicate drug-induced increase in severity of dystonic attacks or decrease in latency to onset of attacks, or combinations of both.

Once the maximum severity of the dystonic attack was reached, the triple stimulation technique used for control and drug experiments induced a typical sequence of dystonic movements that was subdivided into six stages as described by Löscher et al. (37). For grading of the dystonic movements, the hamsters were observed in the empty cage for 3 h and the severity of the dystonic attack was rated as follows: stage 1, flattened ears and flattened posture while walking, preceded by wet-dog shakes, grooming, and rapidly twitching vibrissae; stage 2, facial contortions, rearings with forelimbs crossing, disturbed gait with retarded setting of forepaws; stage 3, stiffened hindlimbs so that the animals appeared to walk on tiptoes in a dysmetric hypergait; stage 4, twisting movements and loss of balance; stage 5, hindlimbs hyperextended caudally, animal continued to pull itself with the functional forelimbs; stage 6, animal immobilized in a twisted, hunched posture with both hindlimbs and forelimbs tonically extended forward, Straub tail, opisthotonus, alternating unilateral forelimb elevation, swaying movements of the head, and copious red eye mucus and salivation. This final stage persisted for 2–5 h, but rapid recovery occurred thereafter. Not all mutant hamsters progressed through the entire sequence described; the individual maximum stage was usually reached within 45–170 min. Electromyographic (EMG) and electroencephalographic (EEG) recording before, during, and after dystonic attacks showed that the onset of the attack coincided with continuous tonic muscle activity and phasic bursts, which were

present even when the animals did not move, whereas the EEG showed no abnormalities (37).

For drug testing, a control trial was undertaken with the triple stimulation technique, injecting the vehicle used for drug administration (see subsequent description), and the latency and severity of the dystonic attack were noted after placing the animals in the new cage (predrug 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 adverse effects of test drugs. Two days later, a control trial with the triple stimulation technique was undertaken (postdrug control). Hamsters that differed in the maximum severity of dystonic movements in the predrug and postdrug control trials by more than two stages were omitted from the drug evaluation. In the present experiment, 40 of 295 dystonic hamsters could not be used for final evaluation because of such a variation between pre- and postdrug control data.

The following doses of drugs were administered IP in groups of nine to 17 mutant hamsters: 8-OH-DPAT, 0.1, 1, and 5 mg/kg; 5-MeO-DMT, 1, 2, 3, and 5 mg/kg; ipsapirone, 5 mg/kg; (+)-WAY-100135, 5 and 10 mg/kg; SDZ 216-525, 1 and 10 mg/kg; pindobind-5-HT_{1A}, 1 mg/kg; pindolol, 2 mg/kg; DOI, 1 mg/kg; and ritanserin, 2.5 and 5 mg/kg. These doses were chosen on the basis of previous studies with these drugs in rodents (11,20,21,24,29–31,33,35,51,52,56). Although some of the drugs, particularly 8-OH-DPAT, were injected by the subcutaneous (SC) route in several of these previous studies, we used the IP route for all drugs tested in this study, because previous experiments of our group have demonstrated that there is no difference in the type or extent of behavioural effects between SC and IP injection of 5-HT receptor ligands such as 8-OH-DPAT (33). Some additional doses of drugs, which were available only in limited amounts, were tested in smaller groups of animals (see Results). Furthermore, some drugs were also injected in age-matched nondystonic control hamsters to study whether differences in type, extent, and duration of behavioural effects produced by manipulation of serotonergic neurons existed between dystonic and nondystonic hamsters. The extent of behavioural alterations was scored as recently described for rats (33).

Drugs

The following drugs were generously provided by pharmaceutical companies: 8-OH-DPAT and ipsapirone (Tropon, Köln, FRG), (+)-WAY-100135 (Wyeth Research Ltd., Maidenhead, Berkshire, UK), SDZ 216,525 (Sandoz Pharma Ltd., Basle, Switzerland), and ritanserin (Janssen, Beerse, Belgium). Pindolol was purchased from Sigma (Munich, FRG) and pindobind-5-HT_{1A} and DOI (used as HCl) from RBI (Biotrend, Köln, FRG). 8-OH-DPAT, 5-MeO-DMT, (+)-WAY-100135, pindolol, pindobind-5-HT_{1A}, and DOI were freshly dissolved in distilled water (partly by means of dilute HCl) before each experiment. When dilute HCl had to be used for drug solutions, the pH of the solution was adjusted to about 7.4. Ipsapirone was dissolved in 30% polyethylene glycol 400. Ritanserin was dissolved in ethanol, then diluted with water to a final solvent concentration of 50% (further dilution resulted in drug precipitation). In some additional experiments, ritanserin was administered as solution in 10% cremophore to exclude the possibility that behavioural effects of ritanserin in ethanol were due to an interaction between the pharmacologic effects of ritanserin and ethanol. SDZ 216-525 was suspended

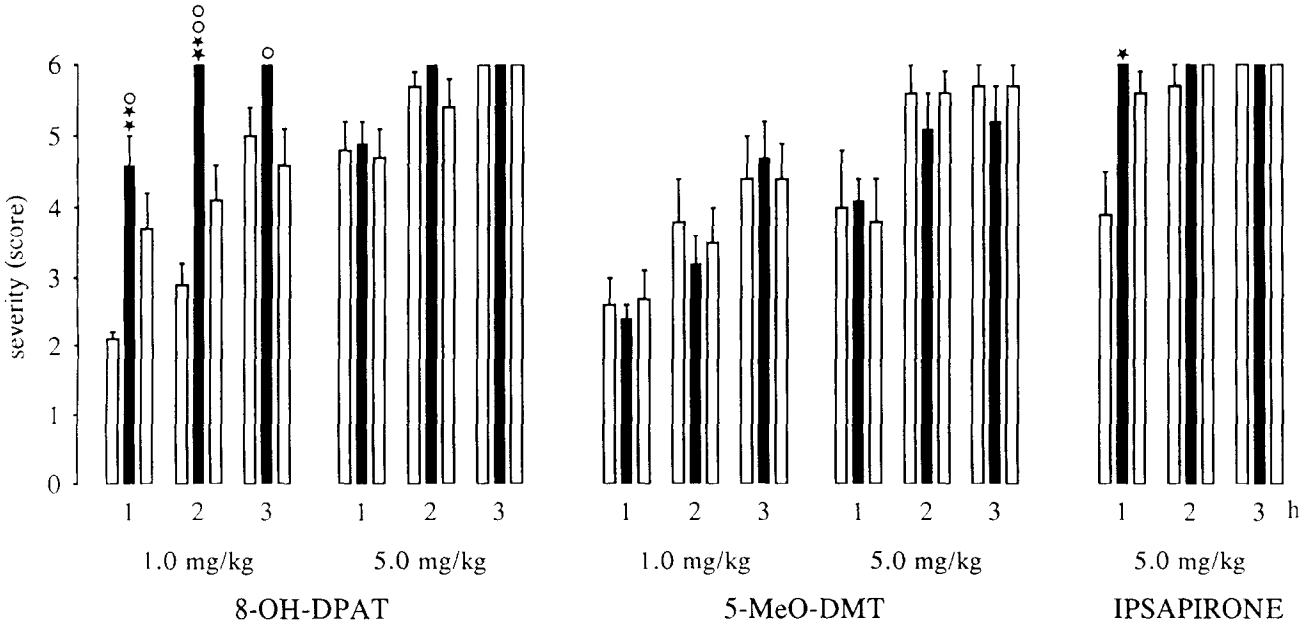

FIG. 1. Effect of full or partial 5-HT_{1A} receptor agonists (8-OH-DPAT, 5-MeO-DMT, and ipsapirone) on dystonic movements in dt^{sz} mutant hamsters at the age of maximum severity of dystonic attacks (30–40 days, max period). Shown is the average of the maximum individual severity scores of dystonic attacks reached within the 1st, 2nd and 3rd h after IP drug administration (black bars). Control recordings (open bars) were taken 2 days before and 2 days after each drug trial. *Significant alterations in the severity of dystonic attacks in comparison with predrug control (*$p < 0.05$; **$p < 0.01$). ○Significant alterations compared with the postdrug control recordings (○$p < 0.05$; ○○$p < 0.01$). Data are shown as means ± SE of nine to 11 hamsters per drug and dose. Absence of SE bars indicates that all hamsters had reached the same severity scores.

in 10% cremophore. For all drug injections, injection volume was 5 ml/kg (2.5 ml/kg in the case of ritanserin in ethanol). Control injections were done with the vehicle used for the respective drug.

Statistics

The significance of differences between control trials (pre- and postdrug) and drug trial in the same group of animals was calculated by the Friedman test and, when a significant difference was found (at least $p < 0.05$), the Wilcoxon signed rank test for paired replicates was used post hoc to determine which pairs differed.

RESULTS

Drug Effects on the Behavioural Syndrome of the Genetically Dystonic Hamster

In dystonic hamsters at the age of maximum severity of dystonia (max period), the 5-HT_{1A} receptor agonist 8-OH-

TABLE 1

EFFECT OF 5-HT RECEPTOR AGONISTS AND ANTAGONISTS ON LATENCY TO ONSET OF DYSTONIC ATTACKS IN MUTANT DYSTONIC HAMSTERS

Drug	Dose (mg/kg, IP)	Latency Onset (min)	
		Predrug Trial	Drug Trial
8-OH-DPAT			
Max	1.0 (n = 10)	19.6 ± 3.1	17.3 ± 2.7
	5.0 (n = 9)	11.1 ± 2.4	6.2 ± 1.1**
Postmax	0.1 (n = 10)	11.2 ± 1.2	8.6 ± 0.9*
	1.0 (n = 10)	17.8 ± 3.0	16.4 ± 1.8
5-MeO-DMT			
Max	1.0 (n = 11)	20.0 ± 3.6	11.9 ± 1.6
	5.0 (n = 9)	18.9 ± 4.0	5.6 ± 0.9**
Postmax	1.0 (n = 8)	24.0 ± 5.9	21.7 ± 5.2
	2.0 (n = 11)	17.8 ± 1.7	9.5 ± 0.9**
	3.0 (n = 12)	16.1 ± 2.5	20.0 ± 1.3
Ipsapirone			
Max	5.0 (n = 10)	20.0 ± 2.4	14.6 ± 1.9
Postmax	5.0 (n = 9)	21.3 ± 5.1	14.1 ± 1.7
(+)-WAY-100135			
Max	5.0 (n = 10)	7.1 ± 0.5	4.3 ± 0.3**
	10.0 (n = 13)	8.0 ± 1.0	2.7 ± 0.3**
Postmax	10.0 (n = 13)	7.9 ± 1.4	2.8 ± 0.4**
SDZ 216-525			
Max	1.0 (n = 9)	8.6 ± 0.8	9.4 ± 0.8
	10.0 (n = 9)	9.0 ± 0.5	10.2 ± 1.3
Postmax	1.0 (n = 11)	6.0 ± 0.9	8.2 ± 0.8
	10.0 (n = 7)	4.4 ± 0.7	7.1 ± 2.0
Pindobind-5-HT_{1A}			
Postmax	1.0 (n = 9)	7.1 ± 0.9	6.9 ± 0.7
Pindolol			
Max	2.0 (n = 9)	5.9 ± 0.5	44.2 ± 7.7**
DOI			
Max	1.0 (n = 11)	11.6 ± 1.8	7.3 ± 0.9*
Postmax	1.0 (n = 11)	14.3 ± 1.7	8.6 ± 1.3**
Ritanserin (in 50% ethanol)			
Max	2.5 (n = 11)	21.0 ± 1.3	12.6 ± 1.3**
	5.0 (n = 8)	11.8 ± 1.1	10.1 ± 1.0
Ritanserin (in 10% cremophore)			
Max	5.0 (n = 9)	8.6 ± 0.7	10.1 ± 0.8
Postmax	2.5 (n = 6)	12.8 ± 2.0	10.0 ± 0.9

Drugs were tested at age of maximum severity of dystonia ("max", 30–40 days of age) and/or at the age of decreasing severity of dystonia ("post-max", 46–52 days of age). Latency was determined as the time to the first unequivocal signs of the dystonic attacks (stage 2). Data are shown as means ± SE of the number (n) of hamsters indicated. Significances to predrug control trials are marked by asterisks (*$p < 0.05$; **$p < 0.01$). It should be noted that although there were differences between individual groups of hamsters in control latencies, the within-group variation of this parameter was very low (not illustrated).

DPAT produced significant prodystonic effects (Fig. 1 and Table 1). Thus, after the administration of 1 mg/kg, the severity of the attack increased and the individual maximum stages were reached more rapidly (Fig. 1). Because of the high pre- and postdrug severity scores, no such effect was seen at 5 mg/kg (Fig. 1), but 8-OH-DPAT significantly reduced the latency to onset of the attacks at this dosage (Table 1). When 8-OH-DPAT was administered in older animals with reduced severity of dystonic attacks (postmax period), 1 mg/kg significantly increased the severity of dystonia (Fig. 2). When the dose was reduced to 0.1 mg/kg, no such effect on severity was seen (Fig. 2), but the latency to onset of attacks was significantly decreased (Table 1). Because of the marked adverse effects induced by 5 mg/kg (see subsequent discussion), this dose was only tested in the max period.

The mixed 5-HT_{1A}/5-HT_2 receptor agonist 5-MeO-DMT did not alter the severity of dystonic attacks in both max and postmax periods (Figs. 1 and 2), although behaviourally active doses were administered (see subsequent discussion). Prodystonic effects were observed with respect to the onset of dystonia in that latencies were significantly reduced by 5 mg/kg (max period) or 2 mg/kg (postmax period), respectively (Table 1). Because of the marked behavioural adverse effect of 5 mg/kg (see subsequent discussion), this high dose was only tested in the max period.

The 5-HT_{1A} receptor partial agonist ipsapirone markedly accelerated the progression of dystonic attacks in the max period (Fig. 1). Thus, the individual maximum severity of attacks was reached within 38.9 ± 2.7 min after ipsapirone compared with 71.4 ± 10.1 min and 51.0 ± 5.4 min in the predrug and postdrug trials ($p < 0.05$). In the postmax period, ipsapirone did not increase the severity of dystonic attacks (Fig. 2) but tended to reduce the latency (Table 1).

The 5-HT_{1A} receptor antagonists (+)-WAY-100135, SDZ 216-525, pindobind-5-HT_{1A}, and pindolol markedly differed in their effects on dystonia (Figs. 3 and 4). (+)-WAY-100135 exerted significant prodystonic effects in both the max and postmax periods. The drug increased the severity of the attacks (Figs. 3 and 4) and decreased their latency (Table 1). In contrast, latencies were not altered by SDZ 216-525 (Table 1). At a dose of 1 mg/kg, this drug tended to increase the severity of attack during the 1st h after administration in the max period (Fig. 3), but no such prodystonic effects were seen at 10 mg/kg or in the postmax period (Figs. 3 and 4). Similarly, pindobind-5-HT_{1A} (1 mg/kg) did not increase the severity of dystonia in the postmax period (Fig. 4). When the dose was increased to 10 mg/kg in four animals of the postmax period, again no alteration in the severity of attacks was seen with this drug (not illustrated). Similarly, at 10 mg/kg, pindobind-5-HT_{1A} did not alter dystonic attacks in the max period (tested in three animals; not illustrated).

In contrast to the selective 5-HT_{1A} receptor antagonists, pindolol caused pronounced antidystonic effects in mutant hamsters (Fig. 3 and Table 1). Thus, this drug reduced the severity of the attacks during 2 h following administration and significantly increased the latency to onset of the attacks. Because of this antidystonic activity seen in the max period, pindolol was not tested in the postmax period.

The 5-HT_2 receptor agonist DOI, 1 mg/kg, accelerated the progression of dystonic attacks in the max period (Fig. 5). Thus, the individual maximum severity of attacks was reached within 48.6 ± 4.1 min after DOI compared to 107 ± 18.3 min and 101 ± 14.2 min in the predrug and postdrug trials ($p < 0.05$). Furthermore, the latency to onset of dystonic attacks was significantly reduced (Table 1). In the postmax period, DOI significantly increased the severity of dystonic attacks (Fig. 6) and reduced the latency (Table 1). The 5-HT_2 receptor antagonist ritanserin, 2.5 mg/kg, did not alter the severity of

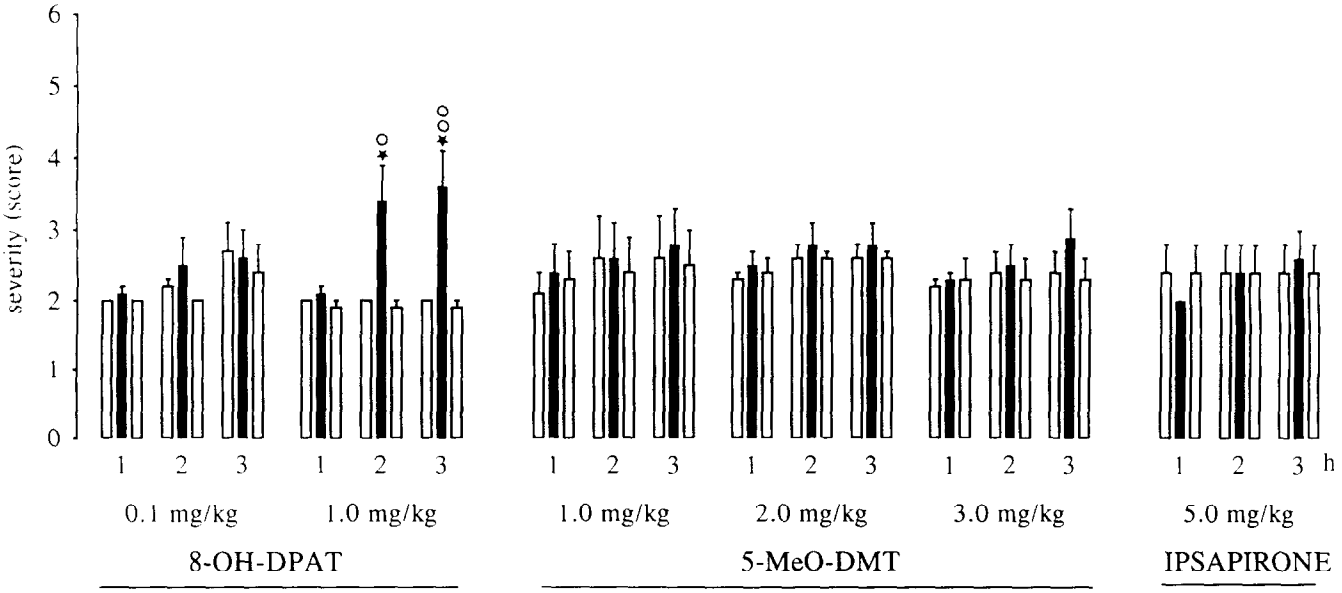

FIG. 2. Effect of full or partial 5-HT_{1A} receptor agonists (8-OH-DPAT, 5-MeO-DMT, and ipsapirone) on dystonic movements in dt^{sz} mutant hamsters after the age of maximum severity of dystonic attacks (postmax period, 46–52 days). Shown is the average of the maximum individual severity scores of dystonic attacks reached within the 1st, 2nd, and 3rd h after IP drug administration (black bars). Control recordings (open bars) were taken 2 days before and 2 days after each drug trial. *Significant alterations in severity of dystonic attacks in comparison with predrug control (*$p < 0.05$). ○Significant alterations compared with the postdrug control recordings (○$p < 0.05$; ○○$p < 0.01$). Data are shown as means ± SE of eight to 12 hamsters per drug and dose. Absence of SE bars indicates that all hamsters had reached the same severity scores.

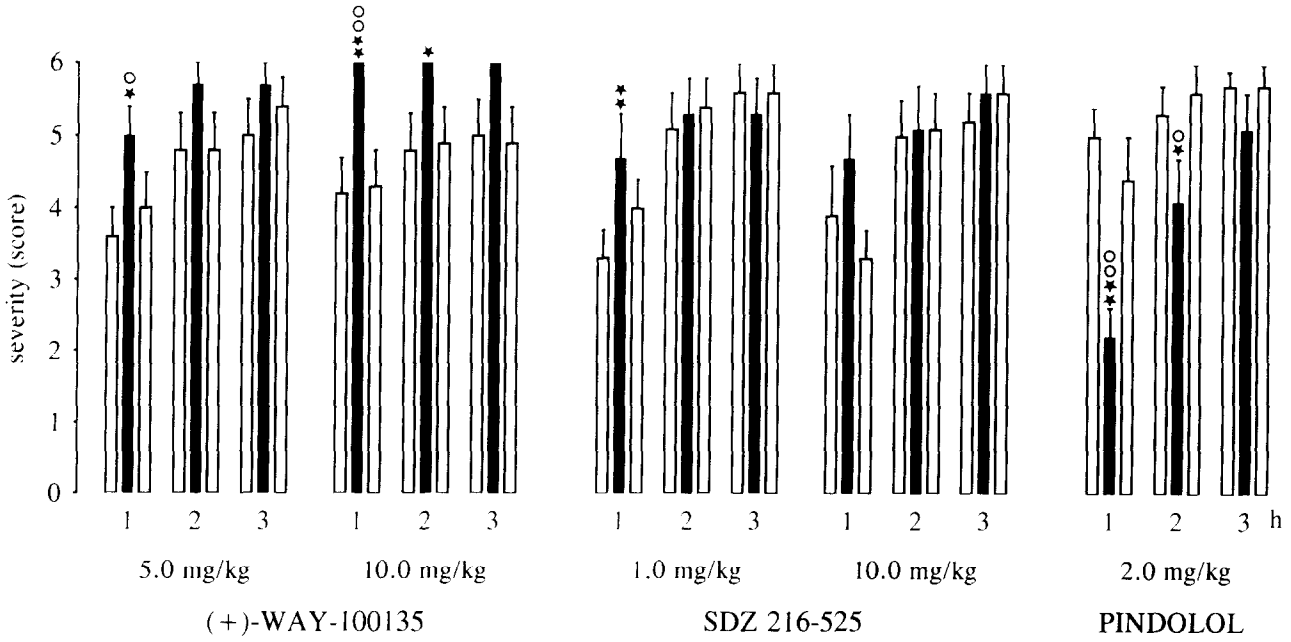

FIG. 3. Effect of 5-HT_{1A} receptor antagonists [(+)-WAY-100135, SDZ 216-525, and pindolol] on dystonic movements in dt^{sz} mutant hamsters at the age of maximum severity of dystonic attacks (30–40 days, max period). Shown is the average of the maximum individual severity scores of dystonic attacks reached within the 1st, 2nd, and 3rd h after IP drug administration (black bars). Control recordings (open bars) were taken 2 days before and 2 days after each drug trial. *Significant alterations in the severity of dystonic attacks in comparison with predrug control (*$p < 0.05$; **$p < 0.01$). ○Significant alterations compared to the postdrug control recordings (○$p < 0.05$; ○○$p < 0.01$). Data are shown as means ± SE of nine to 13 hamsters per drug and dose. Absence of SE bars indicates that all hamsters had reached the same severity scores.

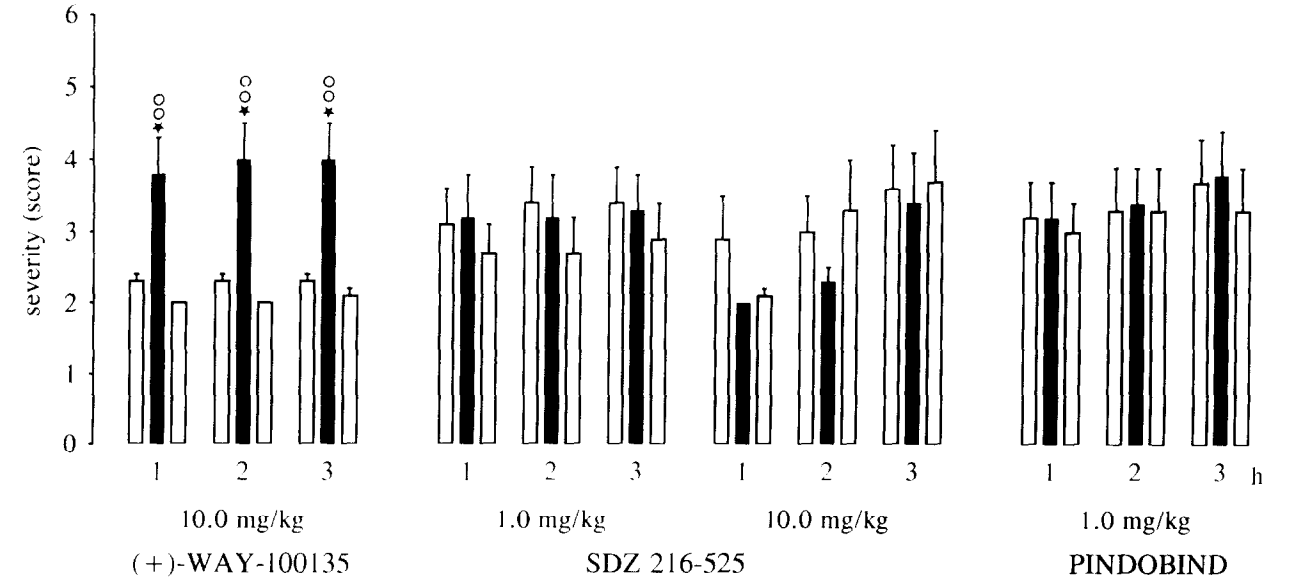

FIG. 4. Effect of 5-HT_{1A} receptor antagonists [(+)-WAY-100135, SDZ 216-525, and pindobind-5-HT_{1A}] on dystonic movements in dt^{sz} mutant hamsters after the age of maximum severity of dystonic attacks (postmax period, 46–52 days). Shown is the average of the maximum individual severity scores of dystonic attacks reached within the 1st, 2nd, and 3rd h after IP drug administration (black bars). Control recordings (open bars) were taken 2 days before and 2 days after each drug trial. *Significant alterations in the severity of dystonic attacks in comparison with predrug control (*$p < 0.05$). ○Significant alterations compared with the postdrug control recordings (○○$p < 0.01$). Data are shown as means ± SE of seven to 13 hamsters per drug and dose. Absence of SE bars indicates that all hamsters had reached the same severity scores.

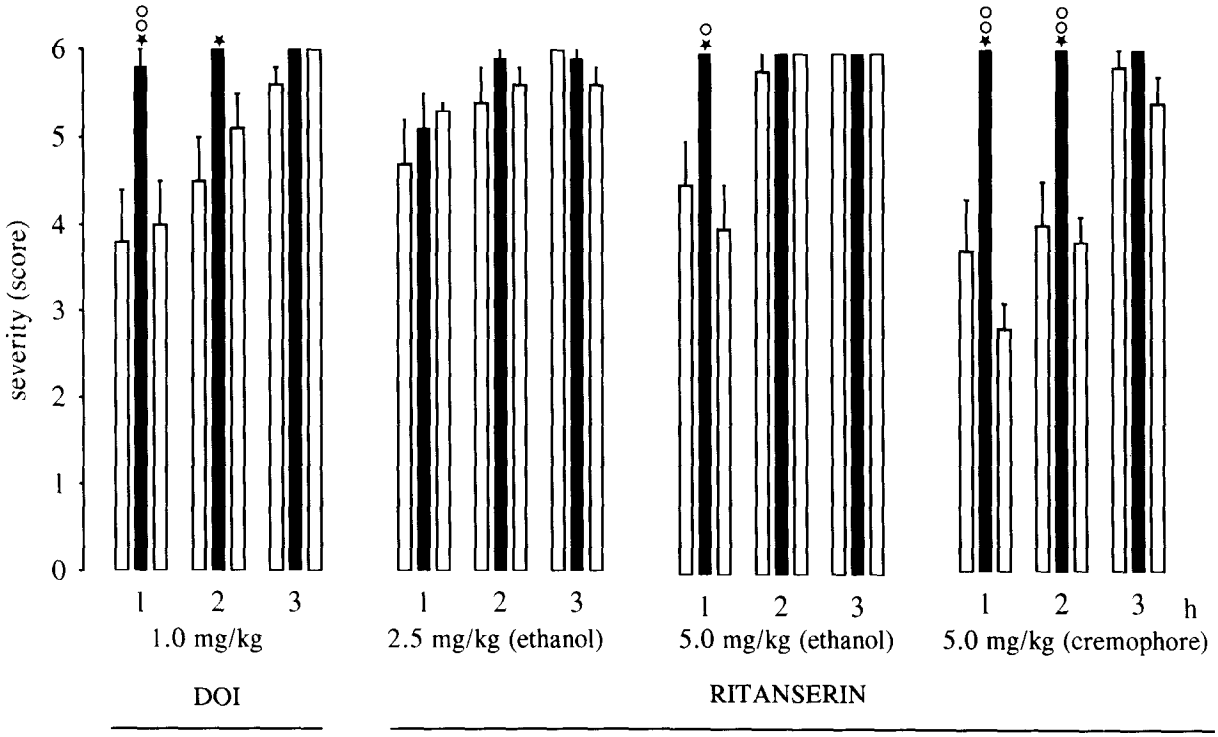

FIG. 5. Effect of the 5-HT_2 receptor agonist DOI and the 5-HT_2 receptor antagonist ritanserin on dystonic movements in dt^{sz} mutant hamsters at the age of maximum severity of dystonic attacks (30–40 days, max period). Ritanserin was dissolved in either 50% ethanol or 10% cremophore. Shown is the average of the maximum individual severity scores of dystonic attacks reached within the 1st, 2nd, and 3rd h after IP drug administration (black bars). Control recordings (open bars) were taken 2 days before and 2 days after the drug trial. *Significant alterations in the severity of dystonic attacks in comparison with predrug control (*$p < 0.05$; **$p < 0.01$). ○Significant alterations compared with the postdrug control recordings (○$p < 0.05$; ○○$p < 0.01$). Data are shown as means ± SE of groups of eight to 11 dystonic hamsters per dose. Absence of SE bars indicates that all hamsters had reached the same severity scores.

dystonic attacks in the max period, but significantly reduced the latency (Fig. 5 and Table 1). When the dose was increased to 5 mg/kg, the progression of dystonic attacks was accelerated (Fig. 5) with a latency to maximum stage of 32.0 ± 4.6 min vs. 87.5 ± 15.5 min and 77.4 ± 7.1 min in pre- and postdrug trials, respectively ($p < 0.01$). To exclude the possibility that the prodystonic activity seen in these experiment was due to an interaction between ritanserin and the ethanol vehicle, the experiment with 5 mg/kg was repeated by administering ritanserin in 10% cremophore. Again, marked prodystonic effects were observed (Fig. 5). A tendency to prodystonic activity was also seen in the postmax period, when ritanserin was injected at a dose of 2.5 mg/kg, dissolved in 10% cremophore (Fig. 6).

Adverse Behavioural Effects

The 5-HT receptor agonists 8-OH-DPAT and 5-MeO-DMT induced marked behavioural alterations in dystonic hamsters that were partly similar to some symptoms of dystonic attacks, but nevertheless could be separated from the attacks because of differences in the specific symptoms (see subsequent discussion) and the different time course of adverse effects and dystonia. 8-OH-DPAT, 1 or 5 mg/kg, induced the typical 5-HT behavioural syndrome, with flat body posture, hyperlocomotion, and abducted hindlimbs. Whereas the flat body posture did not differ from that seen in stage 1 of a dystonic attack, both hyperlocomotion and hindlimb abduction clearly separated 8-OH-DPAT-induced effects from dystonic attacks, in that hyperlocomotion was not seen during dystonia in hamsters and hindlimbs were extended caudally or forward during dystonic attacks but never laterally as was seen with 8-OH-DPAT. In contrast to rats, no forepaw treading was observed in hamsters after 8-OH-DPAT. Additional behavioural effects were salivation, ataxia, and piloerection. These symptoms appeared within 5–10 min after administration and, except for hyperlocomotion, disappeared within 60 min. Pretreatment with WAY-100135 (10 mg/kg), SDZ 216-525 (10 mg/kg), or pindolol (1 mg/kg) antagonized the behavioural syndrome induced by 8-OH-DPAT (tested in older hamsters after remission of dystonia; not illustrated), demonstrating that the compounds acted as antagonists at postsynaptic 5-HT_{1A} receptors in the hamster. Lower doses of 8-OH-DPAT (0.1 mg/kg) were devoid of behavioural adverse effects. In nondystonic animals, the behavioural syndrome induced by 8-OH-DPAT was less marked than in dystonic hamsters.

Behavioural alterations observed after 5-MeO-DMT, 5 mg/kg, were almost identical with those induced by 8-OH-DPAT, 1 or 5 mg/kg. Furthermore, the time course of the 5-HT behavioural syndrome induced by 5-MeO-DMT was similar to the experiments with 8-OH-DPAT. At lower doses, the predominant adverse effect observed after 5-MeO-DMT was flat body posture. Nondystonic hamsters were less sensi-

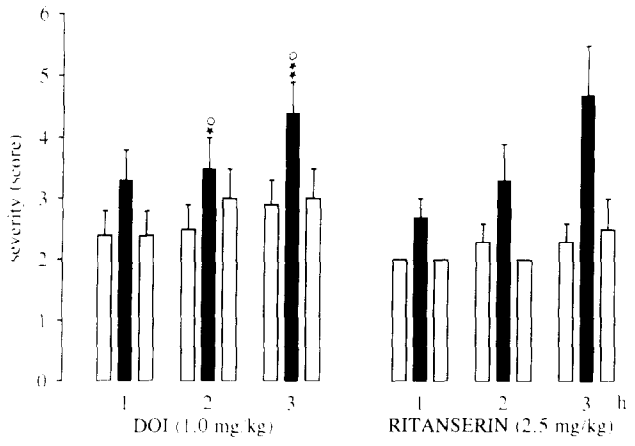

FIG. 6. Effect of the 5-HT_2 receptor agonist DOI and the 5-HT_2 receptor antagonist ritanserin on dystonic movements in *dt*^{sz} mutant hamsters after the age of maximum severity of dystonic attacks (46–52 days, postmax period). Ritanserin was administered as solution in 10% cremophore. Shown is the average of the maximum individual severity scores of dystonic attacks reached within the 1st, 2nd, and 3rd h after IP drug administration (black bars). Control recordings (open bars) were taken 2 days before and 2 days after the drug trial. *Significant alterations in the severity of dystonic attacks in comparison with predrug control (*$p < 0.05$; **$p < 0.01$). ○Significant alterations compared with the postdrug control recordings (○$p < 0.05$). Data are shown as means ± SE of groups of 11 (DOI) and six (ritanserin) dystonic hamsters. The absence of SE bars indicates that all hamsters had reached the same severity scores.

tive to induction of adverse effects by 5-MeO-DMT than were dystonic hamsters.

Ipsapirone, 5 mg/kg, induced flat body posture and hyperactivity for about 30 min. Nondystonic animals showed less marked behavioural alterations in response to ipsapirone.

With (+)-WAY-100135, no adverse effects were noted except hyperaemia of the nose with bloody transudate. After SDZ 216-525, pronounced ptosis was observed. One hamster showed hyperaemia of the nose. Similarly to WAY-100135, the only adverse effect observed after pindobind-5-HT_{1A} was hyperaemia of the nose with bloody transudate (within 20 min after administration). Pindolol induced sedation within 10–15 min after injection for about 60 min.

The major behavioural alterations following administration of DOI, 1 mg/kg, included grimacing, rearing, and marked hyperlocomotion. Grimacing and rearing were seen for about 60 min. Whereas ritanserin itself was devoid of any behavioural adverse effects, the ethanol vehicle (50% ethanol) induced ataxia.

DISCUSSION

In the present study, complex effects of 5-HT receptor ligands were observed in genetically dystonic hamsters. Based on the important role of the brain 5-HT system in the facilitation of motor output (25,55) and neurochemical data showing increased 5-HT turnover in several brain regions of dystonic hamsters (36), our initial expectation was that 5-HT receptor agonists would increase whereas antagonists would decrease the severity of dystonia. However, paradoxically, marked prodystonic effects were seen with both the selective 5-HT_{1A} receptor agonist 8-OH-DPAT and the selective and "silent" 5-HT_{1A} receptor antagonist (+)-WAY-100135; the other 5-HT_{1A} receptor antagonists, SDZ 216-525 and pindobind-5-HT_{1A}, did not alter dystonia to any comparable extent. The only 5-HT_{1A} receptor ligand that decreased dystonia was pindolol, which, however, is also a potent β-adrenoceptor blocking agent. The mixed 5-HT_{1A}/5-HT_2 receptor agonist 5-MeO-DMT exhibited some prodystonic activity (decrease in latency) but, in contrast to 8-OH-DPAT or (+)-WAY-100135, did not alter the severity of dystonic attacks. Similar to 5-MeO-DMT, the partial 5-HT_{1A} receptor antagonist ipsapirone exerted only moderate prodystonic activity. Finally, both the 5-HT_2 receptor agonist DOI and the 5-HT_2 receptor antagonist ritanserin exerted prodystonic activity in mutant hamsters.

How can the differential effects of the three 5-HT_{1A} receptor antagonists—(+)-WAY-100135, SDZ 216-525, and pindobind-5-HT_{1A}—in dystonic hamsters be explained? All three drugs were recently shown in rats to block the 8-OH-DPAT-induced 5-HT behavioural syndrome, in line with an antagonist effect at postsynaptic 5-HT_{1A} receptors (11,29,51). Active doses in this regard were 0.5 mg/kg for pindobind-5-HT_{1A} (29), 0.03–1 mg/kg for SDZ 216-5 (25,51), and 1-10 mg/kg for (+)-WAY-100135 (11). In behavioural studies, none of the three drugs was found to induce partial agonist effects at postsynaptic 5-HT_{1A} receptors (11,29,51), although behavioural effects resembling components of the 5-HT syndrome were recently reported after a high dose (20 mg/kg) of (+)-WAY-100135 in rats (34). With respect to selectivity, the pindolol derivative pindobind-5-HT_{1A} is approximately an order of magnitude less potent at β-adrenergic receptors than at 5-HT_{1A} receptors, whereas pindolol exerts about the same affinity for both receptors (29). Furthermore, compared to its potency at the 5-HT_{1A} receptor, pindobind-5-HT_{1A} was three orders of magnitude less potent or essentially inactive at 10 other neurotransmitter sites analysed, including dopamine- and β-adrenergic sites (29). However, it is not known how pindobind-5-HT_{1A} affects the somatodendritic 5-HT_{1A} receptor. SDZ 216-525, while being a silent antagonist at postsynaptic 5-HT_{1A} receptors, exerts partial agonist effects at the somatodendritic 5-HT_{1A} receptor (12,42,49). Furthermore, the compound shows high affinity for the α_1-adrenoceptor and seems to act as an antagonist at this receptor (12,42,49). Consistent with recent observations in rats (42), SDZ 216-525 induced marked ptosis in the present study in hamsters, a response thought to be mediated by α_1-adrenoceptors. No such effect was seen with pindobind-5-HT_{1A} or (+)-WAY-100135. Indeed, among all presently available 5-HT_{1A} antagonists, (+)-WAY-100135 is considered to be the only selective and silent antagonist at both pre- and postsynaptic 5-HT_{1A} receptors (12).

However, all data on which this assumption is based stem from mice and rats (11,48). In cats, a recent study supported an agonist effect of WAY-100135 at the 5-HT_{1A} presynaptic (somatodendritic) autoreceptor (9). No such data are available for hamsters, but we have recently demonstrated that WAY-100135 antagonizes the 5-HT behavioural syndrome induced by 8-OH-DPAT, demonstrating that WAY-100135 acts as an antagonist at postsynaptic 5-HT_{1A} receptors in the hamster (35). Assuming that—as in other rodent species—(+)-WAY-100135 is a silent ligand at both pre- and postsynaptic 5-HT_{1A} receptors in hamsters, there are several explanations for a prodystonic effect of (+)-WAY-100135 compared to other 5-HT_{1A} receptor antagonists tested. First, possibly as a result of blockade of somatodendritic 5-HT_{1A} receptors, (+)-WAY100135 was shown to increase extracellular levels of 5-HT immediately after drug administration in rats (48). This effect could lead to increased activation of postsynaptic 5-HT

receptors not blocked by WAY-100135, which would also explain the behavioural alterations seen after high doses of WAY-100135 in rats (34). In contrast, partial agonists at presynaptic 5-HT_{1A} receptors, such as SDZ 216-525, decrease extracellular 5-HT_12, which could explain the lack of prodystonic activity in hamsters. Second, a silent 5-HT_{1A} receptor antagonist such as (+)-WAY-100135 would enhance glutamatergic transmission by inhibiting the tonic hyperpolarizing action of endogenous 5-HT at 5-HT_{1A} receptors located on cortical pyramidal glutamate-containing neurons (12). Several lines of evidence suggest that enhanced glutamatergic transmission is involved in dystonia (43,44,46,47) so that such a 5-HT_{1A} receptor-mediated glutamatergic drug effect would be likely to produce prodystonic effects. Although pindolol is also a silent antagonist at pre- and postsynaptic 5-HT_{1A} receptors (12), the lack of prodystonic effects of this drug might be due to its potent β-adrenoceptor blocking activity, which differentiates pindolol from all other 5-HT_{1A} receptor ligands used in this study. This view is corroborated by the fact that several other adrenergic blocking agents, including propranolol, were previously found to inhibit dystonia in genetically dystonic hamsters (45), which would be consistent with an involvement of increased noradrenergic transmission in dystonia as recently indicated by neurochemical data in dystonic hamsters (36). As demonstrated by the present comparison between pindolol and three selective 5-HT_{1A} receptor antagonists, the use of pindolol as a research tool in studies on physiologic roles of 5-HT_{1A} receptors might result in misleading conclusions because of the potent β-adrenoceptor blocking effect of this compound. Furthermore, in addition to β-adrenoceptors and 5-HT_{1A} receptors, pindolol acts as an antagonist at nerve terminal 5-HT_{1B} autoreceptors (12).

Ipsapirone, which behaves as a full agonist at presynaptic and as partial agonist or antagonist at postsynaptic 5-HT_{1A} receptors (17), resembled SDZ 216-525 in its effects in dystonic hamsters. Thus, it accelerated the progression of a dystonic attack in hamsters at the age of maximum severity of dystonia, but was devoid of any effect in older animals. With respect to the prodystonic activity of full or partial 5-HT_{1A} receptor agonists such as 8-OH-DPAT and ipsapirone, it should be noted that such drugs have been shown to increase dopamine turnover in basal ganglia, possibly as a result of decreased 5-HT turnover and/or direct effects on dopamine (auto)receptors (1,4,22). In view of the recent finding that pharmacologic activation of dopaminergic transmission produces prodystonic effects in dystonic hamsters (32), such an action of 5-HT_{1A} agonists/partial agonists would explain their prodystonic activity. Increased striatal dopamine synthesis was also found with 5-MeO-DMT (1). However, 5-MeO-DMT, which in addition to stimulating 5-HT_{1A} receptors (52), exerts a pronounced stimulatory effect on 5-HT_2 receptors (13,19,38), was clearly less prodystonic than 8-OH-DPAT, although the behavioural adverse effects observed after both drugs were similar. One explanation for this apparently paradoxical finding is that concomitant stimulation of 5-HT_{1A} and 5-HT_2 receptors might decrease some functional consequences of 5-HT_{1A} receptor stimulation, such as those involved in prodystonic activity. Indeed, there is some evidence that 5-HT_2 receptor stimulation exerts a tonic inhibitory effect on 5-HT_{1A} receptor function (3).

To further evaluate the functional consequences of 5-HT_2 receptor manipulations in mutant dystonic hamsters, we used DOI and ritanserin (i.e., a standard agonist and antagonist at this receptor subtype) (27). Unexpectedly, both drugs induced prodystonic activity. The prodystonic activity of ritanserin could be explained by assuming that the increased turnover of 5-HT in dystonic hamsters (as recently described by our group) is involved in the induction of dystonic attacks via stimulation of postsynaptic 5-HT_{1A} receptors, and that this action of increased 5-HT levels on 5-HT_{1A} receptors is potentiated through the blockade of 5-HT_2 receptors by ritanserin. In line with this assumption, Backus et al. (3) recently showed that ritanserin increased the 5-HT behavioural syndrome induced by submaximally effective doses of 8-OH-DPAT, 5-MEO-DMT, and gepirone. The present finding that DOI also exerts prodystonic activity would appear to conflict with this assumption. However, similar apparently conflicting data on ritanserin and DOI were also reported by other groups with respect to functional interactions with 5-HT_{1A} receptors, in that both ritanserin and DOI were found to increase behavioural effects of 8-OH-DPAT [e.g., (2,3,14)]. In this respect, it should be noted that most of the ligands currently used to characterize 5-HT receptor subtypes are not completely selective, which, among other factors, explains why the characterization of 5-HT receptor subtype functions and functional interactions between these subtypes is complex and often confusing (18,27). Furthermore, more recent data have indicated that DOI is a partial agonist or mixed agonist-antagonist at 5-HT_2 receptors (7,8), so that, similar to ipsapirone, this drug may behave either as an agonist or antagonist depending on the functional model being used to assess its activity.

A comparison of the present data from genetically dystonic hamsters with data from previous studies in other genetic animal models of dystonia discloses similarities and dissimilarities. In genetically dystonic rats, enhanced susceptibility to behavioural adverse effects of 8-OH-DPAT and the mixed 5-HT_2/5-HT_1 receptor agonist quipazine were found (41,56). Similarly, enhanced behavioural effects were seen with 8-OH-DPAT and 5-MeO-DMT in dystonic hamsters, although the difference to nondystonic controls was not systemically investigated. As far as we know, 8-OH-DPAT, quipazine, and the 5-HT_2 receptor agonist 1-(2,5-dimethoxy-4-bromophenyl)-2-aminopropane are the only 5-HT receptor ligands studied so far in the *dt* rat, so that the effects of 5-HT antagonists in this model are not known. Wieland and Lucki (56) suggested from their data on 5-HT receptor agonists that selective 5-HT_{1A} and 5-HT_2 receptor antagonists would be of therapeutic benefit in the treatment of human dyskinesias. This suggestion is not substantiated by the present and previous data (35) on 5-HT antagonists in the hamster model. In the Wriggle Mouse Sagami (WMS) model of dystonia, ritanserin was shown to reduce abnormal movements (24); this 5-HT_2 receptor antagonist was prodystonic in the present study in genetically dystonic hamsters. Ikeda et al. (24) concluded from their neurochemical and pharmacologic studies that a presynaptic hyperactivity of the serotonergic neural system has an important role in the manifestation of involuntary movements in the WMS, whereas the present data seem to argue against such a suggestion for the dystonic hamster model.

In conclusion, the results of the present series of experiments indicate that dystonia is not a potential clinical application for selective 5-HT_{1A} or 5-HT_2 receptor antagonists. The lack of antidystonic activity of 5-HT antagonists separates these drugs from dopamine, acetylcholine, noradrenaline, and glutamate receptor antagonists, which have been demonstrated to exert antidystonic effects in both genetically dystonic hamsters (32,45–47) and patients with idiopathic dystonia (40,43). Because agonists/partial agonists at presynaptic 5-HT_{1A} receptors such as ipsapirone and SDZ 216-525, which potently decrease 5-HT turnover and/or release (17,21), ex-

hibited no antidystonic activity, it may be concluded that the antidystonic efficacy of benzodiazepines previously found in animal models of dystonia (15,37,39) as well as subgroups of dystonic patients (40) is not related to decreased 5-HT turnover. Furthermore, as demonstrated previously (35) and again by the present data, silent 5-HT_{1A} receptor antagonists such as (+)-WAY-100135 bear the risk of aggravating dystonia, most probably by increasing extracellular levels of 5-HT. Although the clinical relevance of these experimental findings is not clear, the potent prodystonic effect of WAY-100135 clearly detracts from its potential use as a therapeutic agent (12).

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