Pharmacology Biochemistry & Behavior, Vol. 37, pp. 129–133. © Pergamon Press plc, 1990. Printed in the U.S.A. 0091-3057/90 $3.00 + .00

Enhanced Sensitivity to Quipazine in the Genetically Dystonic Rat (*dt*)

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Received 4 June 1990

MICHELA, V. L., S. E. STRATTON AND J. F. LORDEN. *Enhanced sensitivity to quipazine in the genetically dystonic rat* (dt). PHARMACOL BIOCHEM BEHAV **37**(1) 129–133, 1990.—Both normal and genetically dystonic (*dt*) rats show a high-frequency forepaw tremor in response to systemic administration of the serotonin (5-HT) agonist quipazine at 8 days of age. The response declines with age in normal, but not dystonic, rats. By 16 days of age and after the development of a generalized movement disorder, the dystonic rat exhibits enhanced sensitivity to the tremorogenic effects of the drug in comparison with normal rats. Tremor was blocked by pretreatment with ketanserin, suggesting that it is mediated by 5-HT_2 receptors. The dystonic rat has previously been shown to be insensitive to the tremorogenic effects of harmaline, a drug presumed to act indirectly through serotonergic neurons. This finding, coupled with the increased sensitivity to quipazine, suggests the presence of an abnormality in serotonergic systems in the mutants. Since there is evidence of abnormality in the olivo-cerebellar system in the dystonic rat, the alternative hypothesis that a nonserotonergic defect in the olivo-cerebellar system accounts for both the failure of behavioral response to harmaline and the persistent expression of a response to quipazine is also discussed.

Serotonin Quipazine Ketanserin Dystonia Development Tremor

THE genetically dystonic rat (*dt*) is homozygous for an autosomal recessive mutation that results in a generalized motor syndrome with symptoms that become apparent around postnatal day 10 (24). The most characteristic symptoms are twisting of the limbs and trunk, rigid extension of the limbs, and hyperflexion of the trunk. This disease is progressive and significantly impairs locomotion. The *dt* rat represents one of the few animal models of inherited torsion dystonia in man (28). Discovery of the neural basis of the movement disorder observed in the *dt* rat may provide insight into the pathophysiology of analogous human diseases.

Despite the severity of the motor syndrome of the *dt* rat, no signs of lesions or degeneration have been detected in either the central or peripheral nervous system. In the absence of histopathological findings, abnormal pharmacological responses have been sought to provide clues about the locus of the underlying defect. In early studies of the mutants, a variety of compounds with known effects on motor systems were investigated [e.g., (24–26, 29)]. An important difference that emerged between diseased and unaffected littermates was the finding that the mutant rats were behaviorally insensitive to the tremor-inducing drug, harmaline (25).

Normal rats first display tremor in response to harmaline between postnatal days 9 and 12 (18). In *dt* rats, harmaline-induced tremor cannot be reliably detected even in much older animals. The mutant rats do, however, respond to oxotremorine, a cholinergic agonist (8), both before and after the onset of the movement disorder. The frequency and latency of the oxotremorine response is similar in both normal and mutant rats, suggesting that the ineffectiveness of harmaline is not due to an inability of the mutant rats to display tremor (25). Rather these findings suggest that there may be a defect in the specific pathway underlying harmaline tremor, the olivo-cerebello-bulbar system (11,23). The inferior olive, which provides climbing fiber input to the Purkinje cells, is thought to act as the pacemaker for the tremor. Harmaline causes increases in the frequency and rhythmicity of inferior olivary neurons which are reflected in the complex spike activity of the Purkinje cells, the output neurons of the cerebellar cortex. This results in bursts of spikes in the deep cerebellar nuclei and the spinal motoneurons. Biochemical, metabolic, and electrophysiological studies support the view that the cerebellar output of the *dt* rat is abnormal. Glucose utilization, glutamic acid decarboxylase activity and the density of GABA receptors are altered in the deep cerebellar nuclei of the mutant rats in comparisons with normal controls (3, 6, 32). Furthermore, the Purkinje cells in the cerebellar vermis of the mutant rats do not display the characteristic changes in activity caused by harmaline in normal rats (38). In normal rats systemic injection of harmaline results in an increase in the frequency and rhythmicity of complex spike rates and a suppression of simple spike activity in at least two-thirds of the cells sampled. In contrast, fewer than ten percent of the Purkinje cells of dystonic rats showed this response (38). Although the response of the Purkinje cells of the *dt* rat to harmaline is abnormal, the basis for this abnormal response is not understood.

[1]S. E. Stratton was a recipient of an Omnitech Travel Fellowship to the Society for Neuroscience Meeting, 1989. This paper is based in part on her abstract submitted for the award. The award-winning papers are published together in this issue.

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Several lines of evidence suggest that the insensitivity of the mutant rats to harmaline is not due to a failure of the drug to reach the central nervous system. Harmaline administration significantly increases 3′,5′-guanosine monophosphate activity in the cerebellum of normal and *dt* rats (25). In addition, the response of Purkinje cells in the cerebellar hemispheres to harmaline is similar in normal and *dt* rats (38).

Harmaline is structurally similar to serotonin (5-HT) and it has been hypothesized that the effects of harmaline in the inferior olive may depend in part on the presence of serotonergic (5-HT) innervation of the olive. Ontogenetic studies have revealed a significant correlation between the onset of harmaline's effects and the maturation of the 5-HT systems in the rat and rabbit (2,18). The behavioral effects of harmaline can be blocked by pretreatment with 5,7-dihydroxytryptamine, a selective serotonergic neurotoxin, but not by parachlorophenylalanine, the 5-HT synthesis inhibitor (2). Harmaline is also a potent monoamine oxidase inhibitor, although the activation of the olivo-cerebellar system that is believed to underlie harmaline tremor is not thought to rely on this property of the drug (9,12). To determine whether harmaline insensitivity in *dt* rats is related to a defect in serotonergic systems, we examined the effects of quipazine, another tremorogenic drug known to act as a 5-HT agonist (16). Although many serotonergic agonists have motor effects [e.g., (40)], quipazine was selected because it is known to produce a dose-dependent tremor in rabbits as early as postnatal day 1 (2). This effect is blocked by methysergide, but is unaffected by 5,7-DHT treatment. Quipazine may act directly at 5-HT receptor sites rather than through 5-HT-containing fibers, as postulated for harmaline. Studies of the effects of quipazine in other physiological and behavioral systems have also suggested that quipazine's effects are mediated by serotonin receptors, in some cases specifically by 5-HT_2 receptors (14, 16, 31, 35, 43). Thus, the specific questions raised in the present study were whether the *dt* rat was sensitive to the tremorogenic effects of quipazine and whether the tremor was mediated by 5-HT_2 receptors. In addition, we examined the development of quipazine tremor. Since quipazine is effective in inducing tremor at ages prior to the onset of the dystonic syndrome, we attempted to use this drug to distinguish between phenotypes prior to the onset of motor symptoms.

METHOD

Litters of rats containing normal and dystonic pups were obtained from the breeding colony maintained at the University of Alabama at Birmingham. Because their disease is progressive, we use the rats shortly after the appearance of their symptoms in order to study them while their general health is still good. At postnatal day 8, there is no reliable indication of phenotype. By 11 days of age, however, mutant pups can be identified with 75% accuracy, and by day 16, the motor syndrome of the mutants is clearly established. Quipazine maleate (10 mg/kg, Miles Laboratories) was administered IP to dystonic rats and their phenotypically normal littermates at 8, 11, and 16 days of age. This dose was chosen on the basis of both pilot studies in normal and *dt* rats and published work in immature rabbits (2). Animals administered quipazine were observed for forepaw tremor. Tremor episodes were measured to the nearest second as the animals were gently restrained in a supine position for 15-sec intervals. Short observation periods were used throughout the study to minimize stress and body heat loss. Body temperature was maintained between observations by placing animals on a 37°C heating pad. Observations were made 10 min after drug injection.

To determine the limits of sensitivity to quipazine in dystonic rats, three groups of 16-day-old rats were administered low doses of quipazine and observed for forepaw tremor. Groups of eight rats received either 0.05, 0.2, or 0.5 mg/kg of quipazine. Eight additional dystonic rats received injections of the saline vehicle. Eight normals of the same age received the 0.5 mg/kg dose of quipazine. For this study, animals were observed for 30-sec periods before injection and 5, 10, 15, and 30 min postinjection.

Ketanserin tartrate (Research Biochemicals, Inc.), a putative 5-HT_2 receptor antagonist, was used to block quipazine tremor (20). Additional groups of 16-day-old dystonic rats (N = 6/group) were given either ketanserin (5 mg/kg) or an equivalent volume of saline 15 min prior to quipazine administration (10 mg/kg). Rats were observed prior to injections and again 10 and 15 min after ketanserin or the vehicle. The last observation period was immediately prior to the injection of quipazine. Observations were made again 5, 10, 15, 30, and 60 min after quipazine injections. All observations were carried out for 30-sec periods.

To obtain a measure of tremor frequency, 16-day-old dystonic rats were administered 10 mg/kg of quipazine and restrained as for all measurements of tremor. A loop of silk suture was placed around the rat's forepaw and led to a Grass force displacement transducer. The output of the force transducer was recorded on a polygraph.

All behavior was recorded on videotape. Duration of forepaw tremor was converted to a percent of the observation interval for presentation. All data were analyzed by analysis of variance or in the case of repeated measures designs, by multivariate profile analysis. Data used in the analyses were obtained during the observation period. The accuracy of the observations was confirmed by reviewing the tapes.

RESULTS

Quipazine administration produced a high-frequency tremor that could be observed in the forepaws of rats held in a supine position. The tremor is illustrated in Fig. 1 and has a frequency of 18 Hz.

In normal rats, quipazine tremor was readily observable at 8 days of age (Fig. 2). Over the next week of life, however, the response declined. In dystonic rats, no decrement was seen. Analysis of variance indicated that the two groups differed significantly, $F(1,30) = 8.49$, $p < 0.01$. This difference was accounted for by the observations on postnatal day 16. A significant linear trend was obtained only in the phenotypically normal group, $F(1,16) = 15.97$, $p < 0.001$, indicating that the response in this group declined with age. Sensitivity to quipazine appeared to persist beyond postnatal day 16 in the dystonic rats. Four additional rats were tested at postnatal day 25 and were found to be responsive.

The sensitivity of the dystonic rats to quipazine was analyzed in 16-day-old pups (Fig. 3). Saline-treated dystonic rats exhibited a small degree of tremor when compared with normal rats of the same age treated with 0.5 mg/kg of quipazine, $F(1,14) = 7.6$, $p < 0.015$. There were no significant differences among the dystonic groups prior to drug administration (Time 0). A significant effect of drug dose, however, was observed in the mutants, $F(3,28) = 26.96$, $p < 0.0001$. Contrasts between dose groups and the saline control rats indicated that all doses were significantly different from control. At the 0.05 mg/kg dose, however, quipazine-treated rats differed from controls only at the 10- and 15-min time points ($p < 0.05$). Because of the sensitivity of the dystonic rats to quipazine, additional groups of litters were examined with the 0.2 and 0.5 mg/kg doses at postnatal day 8. No difference in responsiveness was detected at the earlier age.

The effects of ketanserin on quipazine-induced tremor in dystonic rats are shown in Fig. 4. Ketanserin alone had no effect

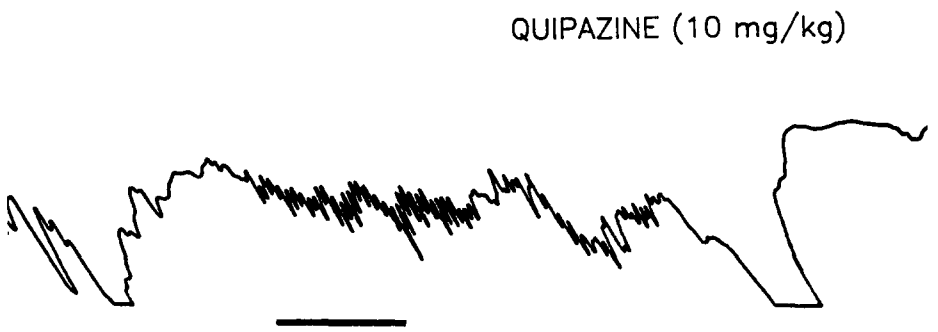

FIG. 1. Polygraph recording of quipazine forepaw tremor from a genetically dystonic rat at 16 days of age. Scale bar = 1 sec.

when compared to saline, $F(1,10) = 0.475$, $p > 0.5$. Following the administration of quipazine, however, a reliable difference was obtained between the groups, $F(1,10) = 47.81$, $p < 0.0001$. At the peak of the quipazine response (15 min postinjection), pretreatment with ketanserin reduced the quipazine tremor by over 60%.

DISCUSSION

Administration of quipazine produces a high-frequency tremor in the forepaws of immature rats. Behavioral studies show that both normal and dystonic rats are sensitive to the effects of quipazine early in development. We were unable to use quipazine to predict the phenotype of pups from the dystonic colony prior to the onset of motor symptoms in the mutants. During the second week of life, however, sensitivity to the drug declines in normal rat pups and is negligible by postnatal day 16. In contrast, the quipazine tremor was elicited over a wide range of doses in dystonic rats at day 16 and later. This effect of quipazine was blocked in dystonic rats by prior administration of ketanserin, suggesting that it is a 5-HT_2 receptor effect.

The enhanced sensitivity of the dystonic rats to quipazine suggests the presence of a serotonergic deficit in the mutants. Experimental destruction of serotonergic neurons leads to supersensitivity to serotonergic agonists, as measured in behavioral assays (41). Enhanced responsiveness to quipazine in the dystonic rats could indicate the presence of a denervation supersensitivity phenomenon. To date, no pre- or postsynaptic deficit has been detected in the 5-HT system of dystonic rats. 5-HT levels, turnover, and receptor binding have been examined but do not differ between normal and dystonic rats (3,26). The results of these biochemical studies rule out the existence of a generalized deficiency in serotonergic systems, but were not sufficiently comprehensive to preclude the presence of a highly localized defect, particularly one limited to the lower brainstem or spinal cord.

Increased sensitivity to serotonergic drugs is a feature associated with several experimentally induced dyskinetic syndromes. Quipazine increases the motor syndrome induced by administration of the toxin iminodipropionitrile (19). This syndrome is believed to result primarily from toxin-induced changes in serotonergic function (7). In addition, several investigators (34,44) have shown that the administration of 3-acetylpyridine (3-AP), a neurotoxin that produces a complex motor syndrome, enhances behavioral sensitivity to 5-HT agonists including quipazine, 5-methoxy-N,N-dimethyltryptamine, 8-OH-2-(di-n-propylamino)tetralin

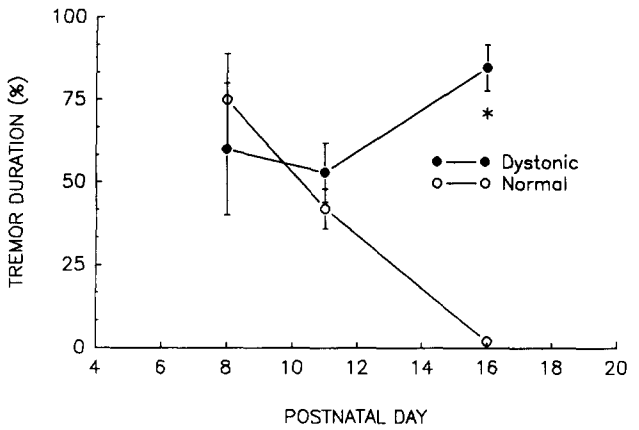

FIG. 2. Forelimb tremor as a function of age for normal and dystonic rats. All rats received 10 mg/kg of quipazine 10 min prior to measurements. Tremor duration is presented as the percentage of a 15-sec observation period during which tremor was detected. Quipazine tremor was significantly reduced in normal rats in comparison with dystonic rats on postnatal day 16.

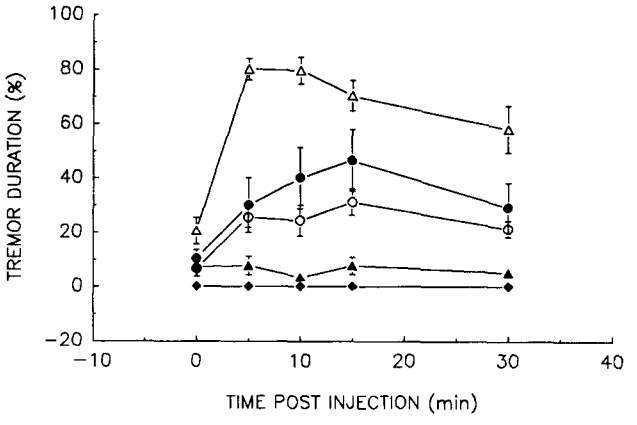

FIG. 3. Dose-response data for quipazine tremor in 16-day-old dystonic rats. Tremor was recorded before and 5, 10, 15 and 30 min after injections of quipazine. Tremor duration is presented as the percentage of a 30-sec observation period during which tremor was detected. Open circles indicate a dose of 0.05 mg/kg; filled circles, 0.2 mg/kg; open triangles, 0.5 mg/kg; and filled triangles, physiological saline. All quipazine groups differed significantly from saline controls. Saline controls also differed from normal rats of the same age (filled diamonds) that received 0.5 mg/kg doses of quipazine.

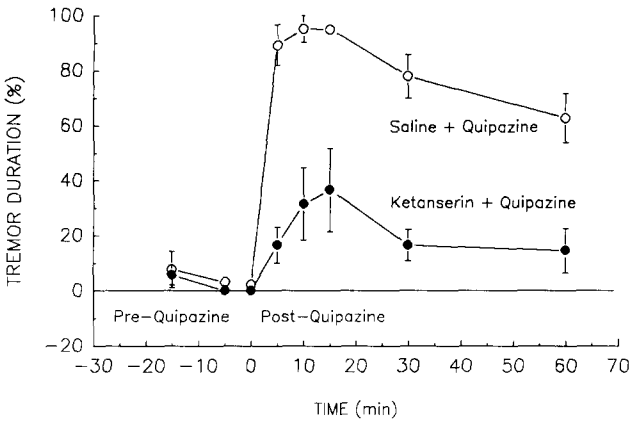

FIG. 4. Quipazine-induced forepaw tremor is plotted for 16-day-old dystonic rats 15 min after pretreatment with ketanserin or physiological saline. Tremor was recorded during 30-sec observation periods 15, 5, and 0 min prior to quipazine injection and again 5, 10, 15, 30 and 60 min postinjection. Ketanserin pretreatment significantly reduced quipazine tremor.

and 1-(2,5-dimethoxy-4-bromophenyl)-2-aminopropane. 3-AP is known to destroy neurons in the inferior olive as well as in a limited number of other central nervous system sites (1,13). Wieland *et al.* (44) have now also shown that there is a decrease in 5-HT immunoreactivity specifically in the nucleus raphe obscurus in 3-AP rats. This loss of immunoreactivity was not, however, associated with any changes in 5-HT or 5-HT_{1A} or 5-HT_2 receptor density. A similar, highly restricted loss of serotonergic neurons or expression of 5-HT in the dystonic rats could be important in the enhanced sensitivity that these mutants demonstrate to quipazine.

The changing sensitivity of normal rats to the quipazine-induced forepaw tremor suggests the maturation of a system that normally functions to inhibit tremulousness. The pathway may be serotonergic, but its identity is at present unknown. Serotonergic agonists, however, have been used to elicit a complex behavioral syndrome that includes hyperactivity, head twitching, resting tremor, reciprocal forepaw treading, hindlimb abduction, and head weaving (17, 34, 35). Ablation studies and intrathecal injections of serotonin suggest that many aspects of the serotonin syndrome are mediated by brainstem and spinal pathways (10,17). Head shaking responses elicited by specific stimulation of 5-HT_2 receptors are also thought to be mediated by brainstem mechanisms (27). Thus, if the difference in the response of normal and dystonic rats to quipazine represents a serotonergic defect, the most likely site of the defect is the brainstem. Others have reported tremors with the same frequency as the quipazine tremor discussed here as resulting from lesions of the cerebellum in early development (15).

The time course for changes in the responsiveness of normal rats to quipazine correlates with the maturation of serotonergic systems in the rat brain. In the rat, most cells giving rise to serotonergic projections undergo their final division and show 5-HT immunoreactivity before birth (21, 22, 42). Innervation of brainstem regions and the development of descending projections to the spinal cord occur by birth (5). Although the pathways are present at birth, serotonergic neurons undergo significant postnatal modification and redistribution (21,22). Functional maturation of the descending serotonergic projections to the spinal cord may not be complete until the third postnatal week (5). This postnatal development of the serotonergic system is reflected in several aspects of behavioral development. Developmental changes in the modulation of the acoustic startle reflex between postnatal days 13 and 17 have been ascribed to changes in central serotonin systems (37). Inhibition of locomotor activity (30) and the loss of suckling from the behavioral repertoire (45) have also been linked to the postnatal maturation of serotonergic systems. At a cellular level, the bursting activity of inferior olivary neurons in response to systemic harmaline administration and the concomitant appearance of sensitivity to harmaline tremor in the rat correlate with the appearance of serotonergic fibers in the inferior olive during the second postnatal week (18,22).

A defect in a specific serotonergic pathway in the dystonic rat is an attractive hypothesis, since it would explain both the absence of a response to the indirectly acting drug harmaline and the increased sensitivity of the mutants to the receptor agonist, quipazine. Quipazine, like harmaline, increases the activity of neurons in the inferior olive (2). Quantitative autoradiographic studies of 5-HT_2 receptors demonstrate the presence of this receptor subtype in the inferior olive (33), suggesting that the inferior olive could serve as a pacemaker for quipazine, as well as harmaline, tremor. Thus, the nucleus reticularis gigantocellularis, the source of serotonergic inputs to the inferior olive (4), stands out as a target for future investigation in the mutant pups.

We have, however, recently shown that harmaline activates the cells of the inferior olive in the mutant rats (39). The postdrug firing rate of olivary cells in the mutant is indistinguishable from that of normal rats, although this activation does not appear to be transmitted to the cerebellar vermis (38). If harmaline's effects are mediated by the serotonergic innervation of the inferior olive, the fact that harmaline can drive the olivary cells of the mutants suggests that the serotonergic innervation of that structure is intact. Since both the behavioral and single unit recording studies in the dystonic rats have examined the effects of systemic administration of harmaline, the results of these studies could indicate that a serotonergic pathway other than that which innervates the inferior olive is abnormal in the mutant rats. For example, the serotonergic projection to the cerebellar cortex rather than the inferior olive may be abnormal.

Until a biochemical defect in a serotonergic system in the mutants can be identified, the existence of a nonserotonergic defect must also be considered. It may be misleading that the dystonic rats respond abnormally to two serotonergic drugs. For example, the dystonic rats may show enhanced motor responses to serotonergic agonists because they lack a completely functional olivo-cerebellar system to suppress the movements stimulated by these compounds. A nonserotonergic defect in the olivo-cerebellar system would also account for the failure of the mutants to respond to harmaline.

In addition to its action on serotonergic systems, quipazine may exert effects at dopaminergic sites. In drug discrimination studies, haloperidol has been shown to block the quipazine-induced responses (36). Dystonic rats have previously been shown to be insensitive to the cataleptic effects of haloperidol, although no evidence of abnormality has been detected in dopaminergic systems at a biochemical level (29). The effectiveness of ketanserin in suppressing the quipazine-induced tremor suggests that this behavioral phenomenon is primarily serotonergic. It is possible, however, that the insensitivity of the mutant rat to haloperidol is functionally linked to its enhanced sensitivity to quipazine. Abnormal cerebellar output, for example, could alter the motor response to haloperidol as well as to quipazine.

ACKNOWLEDGEMENTS

Supported by a grant from the Dystonia Medical Research Foundation and NIMH predoctoral fellowship MH09735 to S. Stratton. Presentation of part of this work at the 1989 Annual Meeting of the Society for Neuroscience was made possible by a travel grant from Omnitech Instruments to S. Stratton.

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