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The Hypothyroid Rat as a Model of Increased Sensitivity to Dopamine Receptor Agonists

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CAMERON, D. L. AND A. D. CROCKER. *The hypothyroid rat as a model of increased sensitivity to dopamine receptor agonists.* PHARMACOL BIOCHEM BEHAV **37**(4) 627–632, 1990.—Control and hypothyroid rats were challenged with a range of doses (0.5–4 μmol/kg) of either the nonselective dopamine agonist, apomorphine, or the selective D2 receptor agonist, LY 171555, and their stereotyped head-down sniffing (SHDS) responses measured. The dose-response curves for both agonists were shifted to the left in the hypothyroid rats compared to water-treated controls. Increasing doses of the selective D2 antagonist, raclopride, caused a parallel shift to the right in the LY 171555-induced SHDS dose-response curve. Schild analysis revealed a decreased sensitivity to raclopride in the hypothyroid animals. The selective D1 antagonist SCH 23390 was observed to decrease the maximal response elicited by LY 171555 in a dose-dependent manner and the hypothyroid rats were more sensitive to this effect. It was concluded that hypothyroid rats showed an apparent increased sensitivity to D2 receptor agonists and a decreased sensitivity to D2 antagonists. In addition, the facilitation effect of the D1 receptor on the D2 receptor appeared less tightly coupled in the hypothyroid rats.

Dopamine Behaviour D1 receptor D2 receptor Thyroid hormones Hypothyroidism Agonist sensitivity Rat

SITUATIONS in which receptor-mediated responses are altered are of great interest as they may provide insight into pathologies that are manifested in the same way. Altered thyroid status has been shown to change the biochemical and behavioural responses to various receptor agonists (14, 18, 19, 22, 25, 28). The aim of this study was to explore the changes in dopamine agonist sensitivity brought about as a consequence of hypothyroidism. The hypothyroid condition was chosen as it most closely parallels the hypothesised changes in dopamine receptor function observed in schizophrenia (21, 24, 26). Previous studies (12, 18, 23) have examined the effects of hypothyroidism on behavioural responses to dopamine receptor agonists and antagonists but did not obtain quantitative pharmacological data. In addition, with the exception of a few studies (12,23), little attention has been given to the verification of the hypothyroid state. Therefore, a clear picture has yet to emerge in relation to the differential effects of the hypothyroid state on responses mediated through the D1 or D2 receptor subtypes. In this study we report the changes in pharmacological response parameters to dopamine receptor agonists in animals with confirmed hypothyroidism.

An additional aim of this study was to apply a more "pharmacological" analysis to altered agonist sensitivity in hypothyroid rats. Thus, we have avoided assessing collections of behaviours or "behavioural syndromes," and have restricted our analysis to the parameters of an established monophasic dose-response relationship, i.e., the agonist-induced stereotyped head-down sniffing response. This approach avoids the assumption of a rigid sequential emergence and disappearance of behaviours with dose that are inherent in the collective assessment of coexisting behaviours that often follow polyphasic dose-response relationships (8).

METHOD

Animals

Adult male Sprague-Dawley rats weighing between 200 and 300 g were used for the present study. Animals were housed 10 per cage under constant temperature, humidity and lighting conditions and given food and water ad lib. All experiments were carried out between 0830 and 1130 hours.

Production of Hypothyroidism

Animals were rendered hypothyroid by the addition of propylthiouracil (PTU) to their drinking water. This drug acts by inhibiting the incorporation of iodine into tyrosyl residues, inhibiting the linkage of tyrosyl residues to form thyroid hormone, and in-

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hibiting the peripheral deiodination of T4 to T3 (13,16). PTU (Sigma) was dissolved in 5 M NaOH and then added to 5 l of tap water (final concentration 0.01% w/v) that was then adjusted to pH 9. Control rats were maintained on tap water that had been adjusted to pH 9.

Validation of Hypothyroid State

As the induction of hypothyroidism is associated with a decrease in body temperature (11), the animals' baseline core body temperature was monitored at regular intervals (at least once/week). Core body temperature was measured using a portable digital thermometer with a flexible probe that was inserted 6–8 cm into the animal's rectum. The temperature of the probe was allowed to equilibrate for 1 minute before the temperature was recorded.

At the conclusion of the behavioural studies, animals were sacrificed by cervical dislocation, a blood sample (approximately 5 ml) taken by cardiac puncture, allowed to clot, and then centrifuged and the serum removed. Serum thyroxine (and on two occasions, tri-iodothyronine) was measured by radioimmunoassay at the Department of Clinical Chemistry, The Queen Elizabeth Hospital, Woodville, S.A.

Animals tolerated the addition of PTU to their drinking water well and there was no difference in the volume of drinking water consumed per kg body weight in the PTU-treated groups compared to control groups. A significant drop in body temperature in the PTU-treated group was taken as indication of hypothyroidism and usually occurred at 1 week to 10 days after the start of treatment. The PTU-treated rats failed to gain weight as rapidly as the controls and stabilised at approximately 80% of the mean of the controls body weight. Measurement of serum T4 after sacrifice confirmed that the PTU-treated animals were in fact hypothyroid, with serum T4 levels approximately 12% of the controls. Serum T3 measured in two groups of rats after 3 and 5 weeks of treatment was 20–25% of control values, verifying the establishment of hypothyroidism.

Drugs

The following drugs were used: apomorphine HCl (Sigma), LY 171555 (quinpirole HCl; Lilly Laboratories), SCH 23390 [(R)-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1H-3-benzazepine, maleate; Schering-Plough USA] raclopride (Astra). SCH 23390 was dissolved in a small volume of 0.1% tartaric acid and then made up to the final volume in isotonic saline. Apomorphine, LY 171555 and Raclopride were dissolved directly in isotonic saline. All drugs were made up fresh on the morning of the experiment and were injected in a volume of 1 ml/kg.

Experimental Procedure

Behavioural responses were assessed using the fixed interval momentary sampling method (8). Briefly, the procedure was as follows: Behavioural observation took place in a room illuminated by a dim red light with the animal placed in a perspex chamber measuring 600 × 300 × 300 mm. Animals were observed for a fifteen-minute period at varying times after injection depending on the time of peak effect for each drug which had been ascertained from preliminary experiment. Animals were allowed to habituate to the rating chamber for 10 minutes before behavioural assessment commenced.

Each 15-minute observation period was broken into 20-second sample periods that were marked by an auditory cue from a modified electronic metronome. The sound emitted by this device was low in both frequency and volume so that the animal under observation was not disturbed. At each cue the observers rated the presence or absence, at that precise instant, of stereotyped head-down sniffing (SHDS) behaviour. This behaviour was chosen as a dependent measure as it has previously been shown to exhibit a clear, monophasic dose-response relationship with the agonists employed in this study. In addition, we have demonstrated the construct validity of the SHDS response in relation to the traditional rating scale methods of assessing dopamine agonist-induced stereotyped behaviour (8).

In all experiments the observer was blind to the animal's thyroid status or dose of drug. Interobserver agreement was always greater than 80%. Animals were injected SC in the right flank in the case of apomorphine, LY 171555, and raclopride and IP in the case of SCH 23390.

The responses to apomorphine were observed in the period 15–25 minutes after injection, and for LY 171555, in the period 25–35 minutes after injection. When the antagonists (SCH 23390, raclopride) were used in combination with LY 171555, they were administered 1 hour before the commencement of the rating period. These optimal postinjection observation times were determined empirically from preliminary experiments.

Analysis of Results

Dose-response curves were analysed by computer-based extended least squares curve-fitting (17) which gave an estimate of the variance associated with each of the calculated parameters (i.e., E_o, ED_{50}, E_{max}). Comparisons were then made between these parameters using Student's *t*-test. In addition, Student's *t*-test was used when only two groups were involved in the experimental design. Where comparisons between multiple groups were made, an analysis of variance (ANOVA) was followed by either Dunnett's test for multiple comparisons to a single control mean, or Scheffe's multiple contrast test. Values for ED_{50} were subjected to log transformation before applying any parametric statistical test (15). In all cases a p value of less than 0.05 was accepted as significant. Value are given as mean ± standard error of the mean.

T3/T4 Replacement

In order to verify that the changes in agonist sensitivity observed were due to a deficit in thyroid hormones and not to some nonspecific action of PTU, the reversal of the PTU-induced changes by the replacement of thyroid hormones was examined. PTU-treated animals and their controls were treated with either T3 or T4 (100 μg/kg SC) daily for 2 (T4) or 3 (T3) weeks. Their SHDS response to a median dose of apomorphine (0.65 μmol/kg) was then assessed and compared to PTU-treated and control animals that received vehicle injections for the same period of time.

RESULTS

Responses to Dopamine Receptor Agonists

As stated in the introduction, the SHDS response induced by apomorphine and LY 171555 was chosen as the best indicator of an altered sensitivity to dopamine receptor agonists.

The SHDS response of control and hypothyroid animals to increasing doses of apomorphine was assessed and the E_{max} and ED_{50} values are given in Table 1. Only the ED_{50} value differed significantly ($p<0.05$) indicating an increased sensitivity to apomorphine in the hypothyroid animals. In addition, the increase in sensitivity to an ED_{50} dose of apomorphine could be observed two weeks after treatment with PTU was commenced and reached

TABLE 1

DOSE-RESPONSE PARAMETERS FOR APOMORPHINE- AND LY 171555-INDUCED SHDS IN WATER- OR PTU-TREATED RATS

Drug	Treatment	E_o	ED_{50}	E_{max}
Apomorphine	water	12.7 ± 1.1	0.65 ± 0.01	85.8 ± 3.2
	PTU	14.7 ± 1.8	0.53 ± 0.02*	83.9 ± 1.1
LY 171555	water	15.4 ± 1.9	0.84 ± 0.08	46.7 ± 3.2
	PTU	17.9 ± 2.6	0.46 ± 0.03*	50.2 ± 3.3

*$p<0.05$, compared to water-treated controls (N = 20 animals in each group).

Animals were treated for 5 weeks and their thyroid status confirmed as described in the Method section. (E_{max},E_o % incidence; ED_{50} μmol/kg.)

a peak at five weeks where it remained fairly stable for treatment periods of up to 19 weeks.

Experiments with the selective D2 receptor agonist LY 171555 revealed a similar profile of action. Again, there appeared a shift to the left in the dose-response curve for the SHDS response in the hypothyroid rats compared with controls. The ED_{50} values (Table 1) were significantly different showing an increased sensitivity to this drug in the hypothyroid animals. Although there was a trend toward a greater E_{max} in the hypothyroid group, this failed to reach significance.

Baseline responses (E_o) did not differ significantly between groups for either drug. In addition, pseudo Hill coefficients, calculated to assess the slope of the dose-response curves, did not differ significantly between groups for either apomorphine or LY 171555.

T3/T4 Replacement Experiments

Animals that had been rendered hypothyroid and shown to be significantly different to their control group in the apomorphine- (0.65 μmol/kg) induced SHDS response were subsequently treated

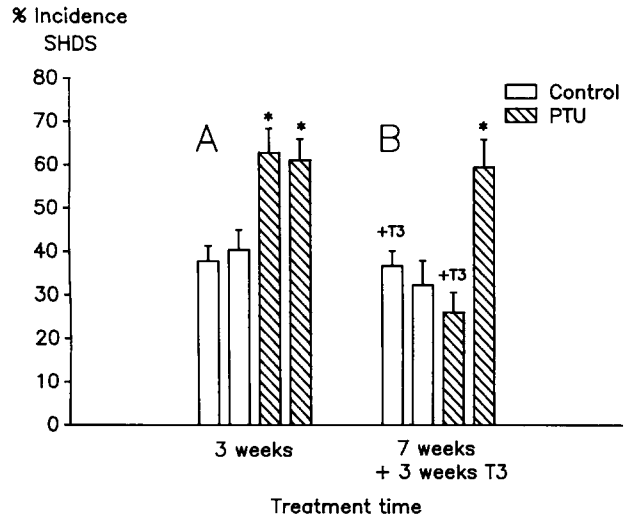

FIG. 1. Apomorphine- (0.65 μmol/kg) induced SHDS in control and PTU-treated animals before (A) and after (B) the daily administration of T3 (100 μg/kg SC) for 3 weeks. Each value represents the mean ± s.e.m. of 8 observations. *$p<0.05$ compared to water-treated control.

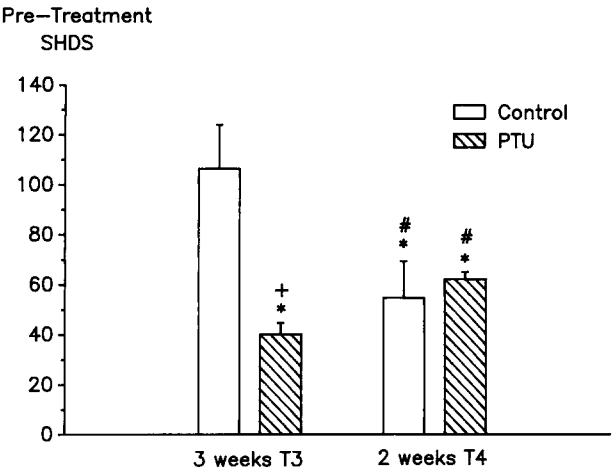

FIG. 2. Apomorphine- (0.65 μmol/kg) induced SHDS in control and PTU-treated animals after the daily administration of T3 (100 μg/kg SC) for 3 weeks or T4 (100 μg/kg SC) for 2 weeks. Each value is expressed as % pre T3/T4 treatment baseline and represents the mean ± s.e.m. of 8 observations. *$p<0.05$ compared to pretreatment baseline, #$p<0.05$ compared to T3-treated group, +$p<0.01$ compared to control group.

with 100 μg/kg T3 SC daily for 3 weeks as were a control group. The T3 treatment caused a reduction in the apomorphine-induced SHDS response in the hypothyroid animals to the point where they were no longer significantly different from control animals that had received T3 injections or those that had received vehicle. In addition, the PTU-treated animals were now significantly less sensitive to the effects of apomorphine than the vehicle-injected PTU group (Fig. 1). The T3 treatment did not appear to significantly affect the response of the control group.

The effects of both T3 and T4 administration on the apomorphine- induced SHDS response were compared in both control and PTU-treated rats (Fig. 2). Although the daily administration of T3 (100 μg/kg SC) significantly reduced the response of PTU-treated rats this effect was not observed in the control group. The daily administration of T4 (100 μg/kg SC), however, was accompanied by a significant reduction in the response to apomorphine in both groups.

Responses to LY 171555 Plus Raclopride and SCH 23390

Varying doses of the selective D2 receptor antagonist raclopride (0–0.5 μmol/kg) were given to both PTU-treated and control rats prior to increasing doses of LY 171555 (0–4.0 μmol/kg). Raclopride caused a parallel shift to the right in the dose-response curve for LY 171555-induced SHDS in both groups. Transforming these data to create a Schild plot (Fig. 3) and subsequent linear regression showed a shift in the apparent pA_2 value from 7.2 in control animals to 7.9 in PTU-treated animals. This indicates that the PTU-treated group showed a 5-fold decrease in the apparent affinity of raclopride for accessible D2 receptors in displacing LY 171555. The slopes of the regression lines were 0.62 for the control group and 0.57 for the PTU group.

The effect of the prior administration of the selective D1 receptor antagonist SCH 23390 on LY 171555-induced SHDS in both control and PTU-treated groups was to decrease the maximal response obtained. Increasing doses of SCH 23390 (0–0.5 μmol/kg IP) brought about a progressive decrease in the E_{max} for both groups. The % reduction in E_{max} as a function of SCH 23390

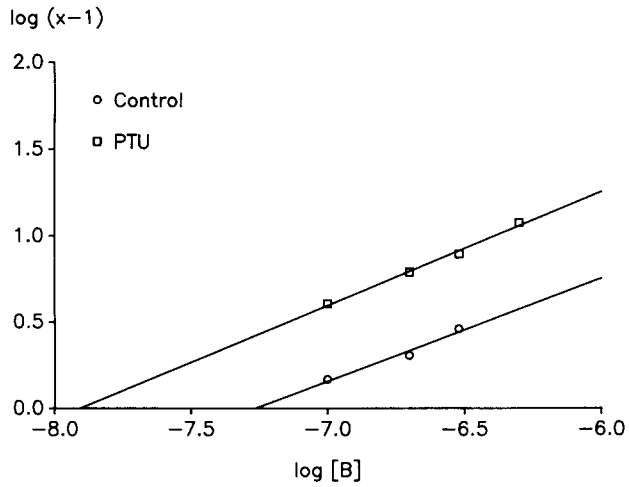

FIG. 3. Schild plot constructed from the antagonist-induced shift in LY 171555-SHDS dose-response curves for hypothyroid and control groups. [B] is the concentration of antagonist (raclopride) while x is the agonist (LY 171555) dose-ratio. Apparent pA_2 values were obtained from the intercepts of the appropriate regression lines with the X-axis. The apparent pA_2 values were 7.2 and 7.9 for the control and PTU-treated groups respectively.

dose is shown in Fig. 4. The degree to which the E_{max} was depressed did not differ between groups; however, the ID_{50} dose of SCH 23390 in the PTU-treated group was significantly different, being approximately half that of the control group (0.021 ± 0.005 μmol/kg vs. 0.056 ± 0.001 μmol/kg; $p<0.05$, n = 30 animals per group).

DISCUSSION

Animals rendered hypothyroid by the addition of PTU to their drinking water showed an increased sensitivity to the mixed D1/D2 dopamine receptor agonist apomorphine as evidenced by a shift to the left of the apomorphine-SHDS dose-response curve.

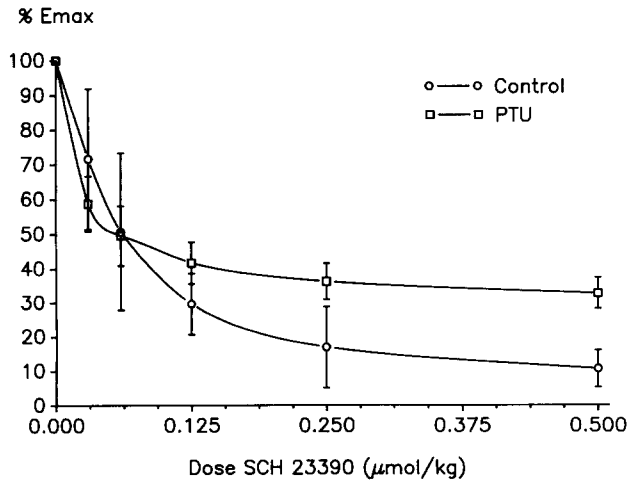

FIG. 4. Increase in maximal LY 171555-induced SHDS as a function of the dose of SCH 23390 in control and PTU-treated animals. Values are expressed as % of maximal response in the absence of SCH 23390. Each point represents the mean ± s.e.m. of 5 observations.

This change in sensitivity was reversed by the daily administration of either T3 or T4 indicating that the results observed were attributable to a deficit in thyroid hormones and not a nonspecific effect of the PTU. Under normal conditions the brain receives its supply of T3 almost exclusively from the local deiodination of T4 (9,10) and so the finding that T3 is able to effect a reversal of the behavioural supersensitivity in the PTU-treated rats may be due to the brain utilising T3 as well as T4 in situations of hypothyroidism. Interestingly, only the T4 treatment had any effect on the behavioural response of the euthyroid controls. As brain T3 receptors are saturated in the euthyroid state (9,10), this observation may point to an additional effect of T4 in the brain that is not mediated via deiodination to T3. The finding of reduced dopamine agonist sensitivity in T4-treated controls is consistent with previous findings (3, 4, 27).

Animals treated with PTU also exhibited an increased sensitivity to the selective D2 agonist LY 171555 which was of a greater magnitude than for apomorphine indicating a predominant effect on the D2 receptor subtype. This could be explained by several possible mechanisms, for example, the change in sensitivity could be due to a change solely in the D2 receptor or a subsequent second messenger. However, given the enabling effect of the D1 receptor on the D2 receptor (1, 2, 20), an alternative explanation is that the relative influence of the D1 receptor on the D2 may be increased in hypothyroidism. This explanation appears unlikely since it predicts that a greater difference would be seen between the groups following apomorphine challenge (where D1 and D2 are stimulated), rather than the LY 171555 challenge (where only D2 are stimulated), and this is the opposite to what was observed. Finally, the most complex explanation is that the changes observed are due to changes in both D1 and D2 receptors and/or their subsequent second messengers. This explanation, however, would also seem unlikely for the same reasons as those outlined above.

In an attempt to distinguish between the alternatives listed above, the D2 receptor was examined in relative isolation by observing the effect of the selective D2 antagonist raclopride on the SHDS response induced by LY 171555. As expected, raclopride caused a dose-dependent parallel shift to the right in the LY 171555-SHDS dose-response curve. This is consistent with raclopride being a competitive antagonist at the D2 site. If the difference in D2-mediated SHDS response was due solely to an increase in tonic D1 facilitation, then one would expect raclopride to exert the same effect on the LY 171555-SHDS response in both groups' baselines (assuming the simplest form of linear interaction between the D1 and D2 receptor). Comparison of the apparent pA_2 values gained from Schild analysis of the results, however, indicates that a change in sensitivity intrinsic to the D2 receptor has occurred. An important caveat, however, is that the assumptions of equilibrium and distribution required to calculate receptor affinities can not be sustained in studies in vivo of this type. Indeed, the slopes of the Schild plots obtained were not unity, indicating a nonequilibrium state. Despite this, apparent values can be used to compare sensitivity between groups and may provide clues as to possible molecular mechanisms and thus provide directions for studies in vitro.

As mentioned above, previous studies (1, 2, 20) have shown that stimulation of the D1 receptor can facilitate responses mediated via the D2 receptor. Therefore, in order to examine the relative effect of the D1 receptor "tone" due to endogenous dopamine on the D2 receptor-mediated response, the effect of the selective D1 antagonist SCH 23390 on LY 171555-induced SHDS was examined. Increasing doses of SCH 23390 brought about a decrease in the E_{max} of LY 171555-induced SHDS. In this experiment, SCH 23390 appeared to act as a noncompetitive antagonist of LY 171555. The degree to which the maximal LY 171555-in-

duced SHDS was depressed with varying doses did not differ significantly between the groups but the ID_{50} for the PTU-treated group was approximately half that of the controls. This result indicates that hypothyroidism does not appear to affect the maximal influence of the D1 receptor on the D2, but that it does alter the D2 receptors sensitivity to D1 facilitation and excludes the difference in D1 "tone" being due to increased endogenous dopamine release. The increased sensitivity of the PTU-treated animals to the SCH 23390 inhibition of LY 171555-induced SHDS indicates that fewer "spare" D1 receptors exist in the hypothyroid animals, pointing to a decrease in the "tightness" or "efficiency" of the coupling between the two receptor subtypes for this interaction.

The question remains as to the molecular mechanism that underlies the changes in agonist sensitivity observed in this study. It is unlikely that this is due to a dispositional change in drug kinetics as this would not account for the opposite sensitivity changes to LY 171555 and raclopride observed in the hypothyroid animals. Previous studies have been equivocal in identifying any changes in receptor concentration or affinity in the striata of hypothyroid rats (5,12). Although changes in dopamine-stimulated adenylate cyclase activity have been reported in the striatal homogenates from hypothyroid rats (5), we have subsequently demonstrated that cAMP is not the second messenger involved in the D2-mediated SHDS response (6).

The possibilities remain, therefore, that the increased dopamine agonist sensitivity observed in hypothyroid rats is due to either 1) an increase in receptor concentration in an extremely small and localised area of the brain that is masked in ligand binding assays, or 2) some change in a neuron downstream from those involved in initiating the agonist response. The former possibility may indeed be likely, as the dopamine receptors responsible for mediating the SHDS response have been identified as having a discrete localisation in the ventral caudate-putamen/dorso-lateral nucleus accumbens (7).

An interesting observation gained from studies using both apomorphine and LY 171555, is that baseline differences between the hypothyroid animals behaviour and their controls was not detected. Differences were only observed after challenge with agonists. This may give us some insights as to the limits of the regulatory mechanisms involved, indicating that some form of compensatory change has occurred in response to hypothyroidism which maintains the animal's normal behaviour, but that this compensation breaks down under agonist challenge.

In summary, animals were rendered hypothyroid by the administration of PTU. The fixed-interval momentary-sampling methodology was applied and provided evidence for an increased sensitivity to the dopamine agonists, apomorphine and LY 171555, in hypothyroidism. Direct evidence for a decrease in D2 receptor antagonist sensitivity in hypothyroid animals was also provided by observing the interaction between the selective D2 agonist LY 171555 and selective D2 antagonist raclopride. In addition, evidence was obtained for a possible decrease in the coupling efficiency of the D1 receptor in its facilitation of D2 receptor-mediated agonist effects in hypothyroid animals. We conclude, therefore, that hypothyroid rats do show increased dopamine receptor agonist sensitivity.

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