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Selective Protection From the Inhibition by EEDQ of D_1 and D_2 Dopamine Agonist-Induced Rotational Behavior in Mice

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GOODALE, D. B., A. G. M. JACOBI, D. M. SEYFRIED AND B. WEISS. *Selective protection from the inhibition by EEDQ of D_1 and D_2 dopamine agonist-induced rotational behavior in mice.* PHARMACOL BIOCHEM BEHAV **30**(2) 457–462, 1988.—Mice with unilateral lesions of dopamine nigrostriatal neurons produced by injecting 6-hydroxydopamine into the striatum exhibited contralateral rotational behavior to the non-selective dopamine agonist apomorphine, the D_1 dopamine agonist SKF 38393, and the D_2 agonist quinpirole. The non-specific dopamine antagonist EEDQ blocked the circling responses to the three agonists. Pretreatment with specific, reversible dopamine antagonists before the EEDQ injection selectively prevented this blockade. Thus, if mice were pretreated with the D_1 receptor antagonist SCH 23390 before EEDQ and the animals challenged with the D_1 and D_2 agonists 24 hours later, the rotational response to quinpirole was still inhibited, but the response to SKF 38393 was now evident. Similarly, in mice pretreated with the D_2 receptor antagonist sulpiride before EEDQ and again challenged with the D_1 and D_2 agonists 24 hours later, the rotational response to SKF 38393 was still inhibited but the response to quinpirole was no longer inhibited. These results indicate that in vivo blockade of either D_1 or D_2 subpopulations of dopamine receptors may be achieved by selective protection with a reversible dopamine antagonist given prior to the administration of an irreversibly acting dopamine antagonist such as EEDQ.

D_1, D_2 Dopamine receptors Dopamine agonists Dopamine antagonists EEDQ Quinpirole LY 171555 SKF 38393 Up regulation Supersensitivity Rotational behavior 6-Hydroxydopamine Selective Protection Apomorphine

DIFFERENT subsets of dopaminergic receptors having different pharmacological properties and which mediate different dopaminergic responses have been shown to be present in the CNS [18, 19, 26, 29], and many pharmacological techniques have been used to identify and characterize these separate receptor systems [4, 8, 10, 30]. Agents having selective affinities for D_1 or D_2 dopamine receptors have been particularly useful [26,30].

SKF 38393 is a prototypic dopamine agonist for selectively activating the D_1 receptors. Administration of SKF 38393 produces a range of biochemical and pharmacological responses unique to D_1 dopamine receptor activation [27, 28, 34]. These responses include: stimulation of dopamine sensitive adenylate cyclase [33], inhibition of ^{3}H-piflutixol binding with no change in ^{3}H-spiperone binding [24], an increase in perioral tardive dyskinesia-like movements in rodents [25], and an increase in contralateral rotation, which is reversed by the D_1 antagonist SCH 23390 but not by the D_2 antagonist sulpiride [1].

Quinpirole (LY 171555) has become the prototypic dopamine agonist for selectively activating the D_2 subset of receptors [32]. The responses typical of D_2 receptor stimulation include: a decrease in serum prolactin, an inhibition of dopamine sensitive adenylate cyclase [32], the production of canine emesis [17], the production of stereotyped behavior [3], an increase in striatal acetylcholine concentration [36], an inhibition of dopamine release, and an inhibition of ^{3}H-spiperone binding with no change in ^{3}H-piflutixol binding [32].

Two pharmacological agents, SCH 23390 [15–17] and sulpiride [1], have been identified as prototypic antagonists for the D_1 and D_2 receptors, respectively. These agents selectively reverse the spectrum of pharmacological effects elicited by the corresponding selective agonists.

In contrast to these selective, reversible agents, a few

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compounds such as N-chloroethyl norapomorphine (NCA) [2], fluphenazine-N-mustard [5,35], and N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) [11] interact irreversibly with dopamine receptors. Of these agents EEDQ has recently been utilized in studying a number of aspects of dopamine receptor functions. In addition to assessing the turnover of dopamine receptors [23] and their localization through autoradiographic techniques [7], EEDQ has been used to study and isolate subgroups of dopamine receptors in the CNS [14, 21, 22].

The present study was designed to determine whether by using selective, reversible D_1 and D_2 antagonists, one can selectively protect these receptors from irreversible blockade by EEDQ in vivo. EEDQ was chosen as the irreversibly acting antagonist because of its well-documented ability to alkylate both D_1 and D_2 receptors in the CNS [11]. Rotational behavior following unilateral nigrostriatal lesions in mice was chosen as a model for assessing the functional activity of dopaminergic receptors because of the involvement of both D_1 and D_2 postsynaptic receptors in this behavior, the ease of quantitation, and the relative lack of subjective evaluations associated with other more complex dopaminergic behaviors.

METHOD

Male, Swiss Webster mice, weighing 23–26 g, were anesthetized with Halothane and placed in a Microtaxic mold designed by Goodale *et al.* [9]. This mold allows the placement of a microliter Hamilton syringe needle directly into the striatum following puncture of the skin, skull and dura with a piercing needle. Since 15–20 mice per hour may be lesioned using this technique, the mold greatly increases the convenience of the lesioning precedure. 6-Hydroxydopamine (16 μg in one microliter of deoxygenated water containing 0.02% L-ascorbic acid) was injected into the striatum at a rate of 1 μl/min, and the needle was left in place for 15 sec after the injection. One week after the intrastriatal injection of 6-hydroxydopamine, mice were administered apomorphine (0.25 mg/kg, SC) to test for rotational behavior. As a screening procedure, only mice with net contralateral rotations of between 20 and 75 rotations per five-minute test period were accepted for further study.

Mice with positive rotational behavior to apomorphine were examined for their responses to the selective D_1 dopamine agonist SKF 38393 and the D_2 dopamine agonist quinpirole. The time interval between the injection of the different dopamine agonists into the same mouse was at least 24 hr.

Rotational behavior was quantitated 15 min after apomorphine and 30 min after quinpirole and SKF 38393. These time points were selected because preliminary experiments showed that maximal rotational responses were observed at these times. The irreversible dopaminergic antagonist EEDQ was administered 24 or 48 hr prior to testing for rotational behavior.

In experiments designed to examine whether selective dopaminergic antagonists could protect from EEDQ-induced inhibition, SCH 23390 or sulpiride was administered 30 or 45 minutes, respectively, prior to EEDQ. The SKF 38393 or quinpirole-induced rotational behavior was quantitated 24 and 48 hr after the administration of EEDQ.

All drugs were administered in a volume of 0.1 mg/10 grams body weight. Apomorphine, quinpirole, and SKF 38393 were dissolved in physiological saline with 0.02% ascorbic acid. EEDQ, SCH 23390, and sulpiride were ground to a fine particle suspension in 0.5% methylcellulose.

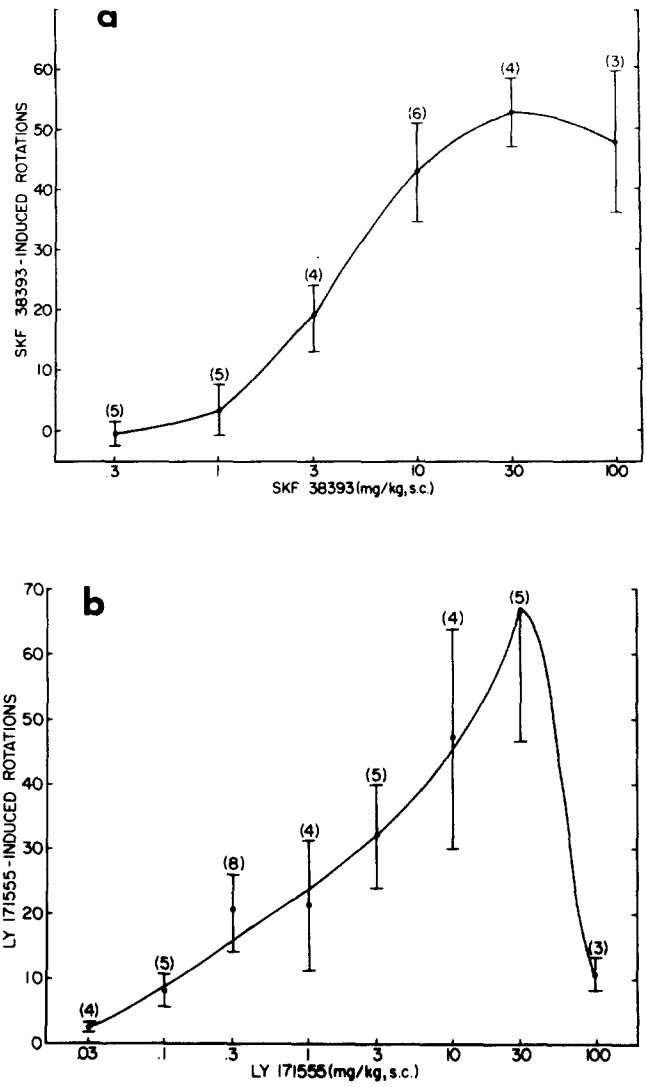

FIG. 1. SKF 38393 and quinpirole-induced contralateral rotations in mice with unilateral nigrostriatal lesions. Varying doses of SKF 38393 (a) or quinpirole (b) were administered subcutaneously to mice. Rotational behavior was quantitated 30 minutes later for a 5-minute period. The symbols represent the means and the vertical lines denote one standard error of the means. Figures in parentheses indicate the number of mice in each group. The ED_{50} value for SKF 38393 was calculated to be 4.3 mg/kg (17 μmol/kg) and the ED_{50} value for quinpirole was calculated to be 1.2 mg/kg (5.6 μmol/kg).

EEDQ was obtained from the Aldrich Chemical Company. SKF 38393 (2,3,4,5-tetrahydro-7,8,dihydroxy-1-phenyl-1H-3-benzazepine hydrochloride) was a gift from Smith Kline & French Laboratories, Philadelphia. Quinpirole (LY 171555) trans-(−)-4,4a,5,6,7,8,8a,9-octahydro-5-propyl-1H (or 2H)-pyrazolo [3,4g] quinoline dihydrochloride) was a gift from Lilly Research Laboratories, Indianapolis, IN. SCH 23390 [(R-)(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1H-3-benzazepine-7-ol] was obtained from Dr. A. Barnett, Schering Corporation, Bloomfield, NJ. Sulpiride (N-[(1-ethyl-2-pyrrolidinyl)methyl]-2-methoxy-5-sulphamoylben-

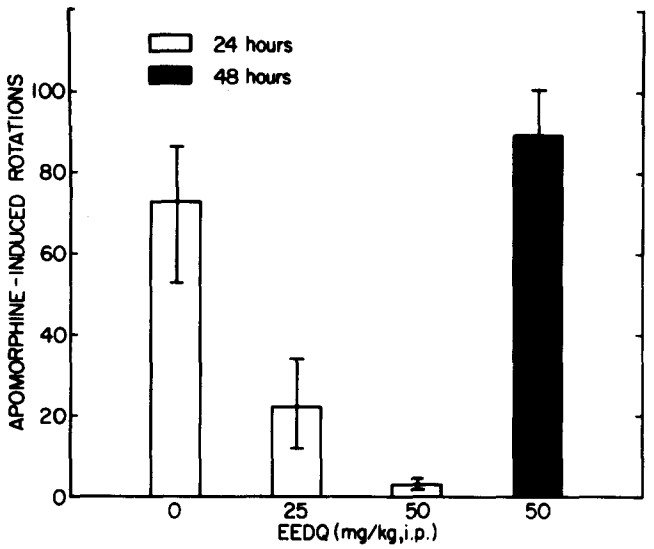

FIG. 2. Inhibition and recovery of apomorphine-induced rotational behavior following treatment with EEDQ. Varying doses of EEDQ were administered to mice showing contralateral asymmetry to a test dose of apomorphine. Either 24 or 48 hours after the EEDQ pretreatment, mice were administered apomorphine (0.5 mg/kg, SC). Rotational behavior was quantitated 15 minutes later for a 5-minute period. The vertical bars represent the means of eight animals, and the vertical lines denote one standard error of the mean. EEDQ inhibited rotational behavior at both 25 mg/kg ($p<0.05$) and 50 mg/kg ($p<0.01$).

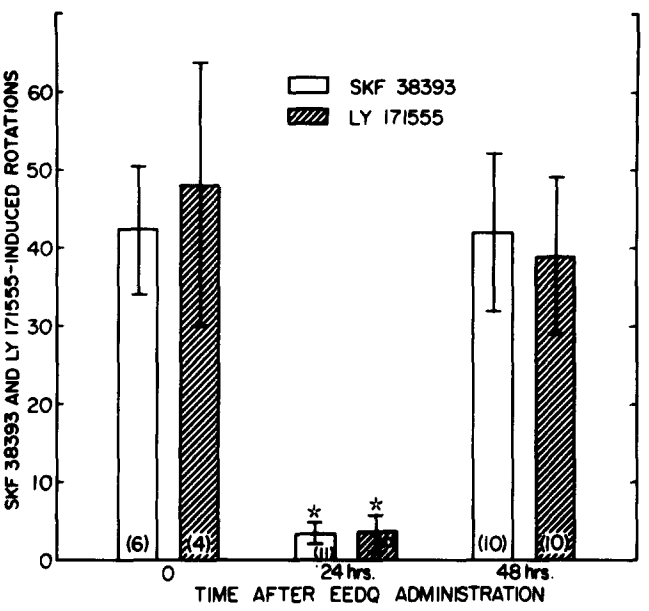

FIG. 3. Inhibition by EEDQ of SKF 38393- and quinpirole-induced rotational behavior in mice. EEDQ (50 mg/kg) was injected intraperitoneally into mice. After either 24 or 48 hr mice were challenged with quinpirole (LY 171555) (10 mg/kg, SC) or SKF 38393 (10 mg/kg, SC). Rotational behavior was observed 30 minutes later for a period of 5 minutes. The vertical bars represent the means and the vertical lines denote one standard error of the means. Figures in parentheses indicate the number of mice in each group. *EEDQ significantly inhibited the response to SKF 38393 and quinpirole ($p<0.01$) when the agonists were given 24 hr after EEDQ. No significant inhibition of the responses was seen if the agonists were given 48 hr after EEDQ.

zamide) was obtained from Sigma Chemical Co., St. Louis, MO.

The data were analyzed by Analysis of Variance using a Tukey-2 post hoc test.

RESULTS

Figure 1a shows the effects of the D_1 agonist SKF 38393 on turning behavior in mice with unilateral 6-hydroxydopamine-induced lesions of the striatum. As may be seen, SKF 38393 produced contralateral rotations in a dose-dependent manner with an ED_{50} of approximately 4.3 mg/kg (17 μmol/kg).

Figure 1b shows the effects of the D_2 agonist quinpirole on rotational behavior in mice. In these experiments, a biphasic curve was observed, with doses of 100 mg/kg causing an inhibition of rotational behavior. At these high doses, mice displayed marked stereotypic head movements and self mutilation behavior.

Figure 2 shows that pretreating mice with EEDQ caused a dose-related inhibition of the rotational response to apomorphine in mice with striatal lesions. This inhibition of apomorphine-induced turning behavior was apparent 24 hr after the administration of EEDQ, but the response returned to control values by 48 hr.

Similar results were seen when the mice were challenged with the selective D_1 or D_2 agonists. Twenty-four or 48 hours after the injection of EEDQ, the mice were administered either SKF 38393 or quinpirole. As can be seen from Fig. 3, the rotational response to both agonists was inhibited 24 hr after EEDQ but had returned to control values by 48 hr after the administration of EEDQ. Zero time values signify that no EEDQ was administered to these mice.

Figure 4 shows the protective effects of selective D_1 or D_2 dopaminergic antagonists on the inhibitory actions of EEDQ. Mice were given either EEDQ alone or with one of the antagonists (either the D_1 antagonist SCH 23390 or the D_2 antagonist sulpiride) 30 or 45 min before the injection of EEDQ. Twenty-four hr after the administration of EEDQ, the mice were challenged with either SKF 38393 or quinpirole. As noted previously, the response to SKF 38393 and quinpirole was inhibited in mice given EEDQ alone. However, if mice were administered the D_1 antagonist SCH 23390 before the EEDQ, the response to the D_2 agonist quinpirole was still inhibited, whereas the response to the D_1 agonist SKF 38393 was no longer blocked. Conversely, when the D_2 antagonist sulpiride was administered before the EEDQ, the subsequent rotational response to SKF 38393 was inhibited, but the response to quinpirole was not significantly different from control values. At 48 hr after EEDQ there was no significant inhibition of rotational behaviors in any experimental group. In fact, there was a statistically significant ($p<0.05$) increase in contralateral rotation induced by SKF 38393 in mice pretreated with SCH 23390 and EEDQ 48 hr before the SKF 38393 challenge. The values were 43±8 rotations per 5 min in animals treated with SKF 38393 alone and 122±36 rotations per 5 min in mice given SKF 38393 48 hr after pretreatment with SCH 23390 and EEDQ.

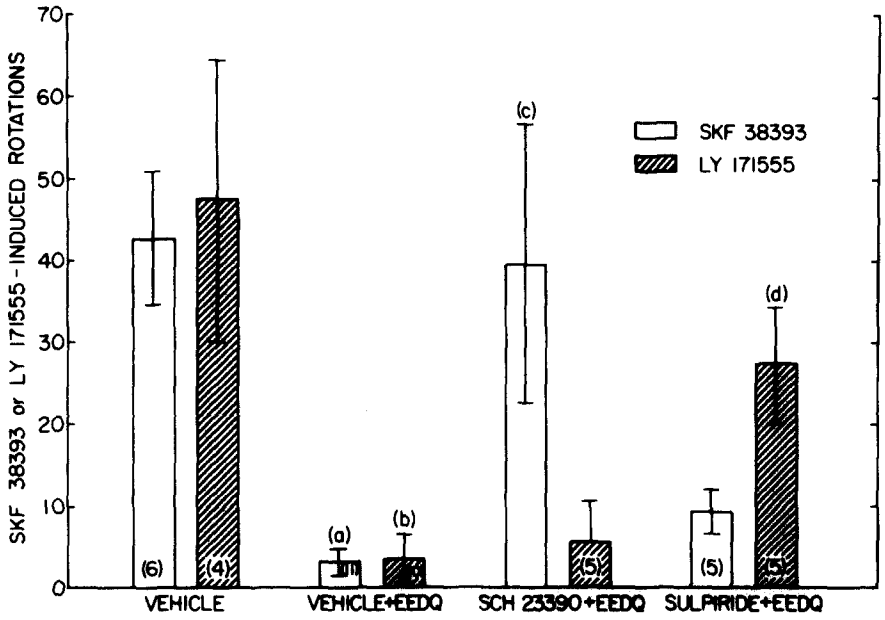

FIG. 4. Selective protection by SCH 23390 and sulpiride from EEDQ-induced inhibition of rotational behavior. Vehicle, SCH 23390 (25 mg/kg, SC) or sulpiride (100 mg/kg, SC) was administered 30 minutes prior to the injection of EEDQ (50 mg/kg, IP). Twenty-four hours after the EEDQ pretreatment, mice were administered either quinpirole (LY 171555) (10 mg/kg, SC) or SKF 38393 (10 mg/kg, SC). Rotational behavior was quantitated 30 minutes after SKF 38393 or quinpirole for a period of five minutes. The vertical bars represent the means and the vertical lines denote one standard error of the mean. The figures in parentheses indicate the number of mice in each group. (a) $p<0.001$ compared with response to SKF 38393 in vehicle-treated mice; (b) $p<0.01$ compared with response to quinpirole in vehicle-treated mice; (c) $p<0.02$ compared with responses to SKF 38393 in mice with EEDQ treatment alone; (d) $p<0.005$ compared with response to quinpirole in mice with EEDQ treatment alone.

DISCUSSION

Mice with unilateral lesions of the corpus striatum induced with the neurotoxin 6-hydroxydopamine provide a useful model for the functional in vivo assessment of postsynaptic striatal dopaminergic responses. Using a recently developed Microtaxic injection mold [9] up to twenty mice may be lesioned in one hour, making feasible the large numbers of unilaterally lesioned animals needed for the present studies.

The D_1 agonist SKF 38393 produced a dose-related increase in contralateral rotational behavior. However, the rotational response to the D_2 agonist quinpirole was somewhat different in that high doses of the agonist produced less rotational behavior than did optimum doses. This may have been due to the marked stereotypic behaviors induced by high doses of quinpirole. In other respects the contralateral rotational behavior seen in responses to SKF 38393 and quinpirole is consistent with previous studies performed in rats [1].

EEDQ blocked the rotations induced by apomorphine as well as by the specific D_1 and D_2 agonists indicating its nonselective effects on dopamine receptors. It may be noted that higher doses of EEDQ were required to block apomorphine-induced rotational behavior than other behaviors such as catalepsy and stereotypic behavior [11]. Although there may be many explanations for this, perhaps higher doses of EEDQ are needed to antagonize behaviors mediated by supersensitive dopamine receptors than those mediated by normosensitive receptors.

Another difference between the results with EEDQ found in the present study with those of earlier studies which used rats is the higher rate of mortality observed in those earlier studies [11]. Hamblin and Creese [11] reported that EEDQ at doses of 10 mg/kg killed 21 of 42 rats, whereas in the present studies doses of EEDQ as high as 50 mg/kg failed to kill any mice. Although this may be related to the differences in species studied, it may also be attributable to the relatively high toxicity of ethanol/propylene glycol (LD_{50} of propylene glycol=13 ml/kg IP in rats; Merck Index) which was used in the studies of Hamblin and Creese [11].

Studies of the time course for recovery of rotational behavior following a single treatment with EEDQ showed that complete recovery occurred by 48 hr. This rate of recovery of dopaminergic behavior was faster than the recovery of dopamine receptors following their irreversible inhibition [11, 20, 23]. This suggests a dissociation between dopaminergic behavior and dopaminergic receptors as measured by radioligand techniques, a conclusion that has been reached in other studies using the irreversible dopaminergic antagonist fluphenazine-N-mustard [31]. The present results emphasize again the difficulty of relating behavioral super- and subsensitivity of the dopaminergic system with the density of dopamine receptors.

The relative rapid rate of recovery of rotation in mice after EEDQ may be explained by the possibility that full occupancy of dopaminergic receptors may not be necessary for full expression of circling behavior. In support of this hypothesis, Meller *et al.* [22] reported that as little as 17% active dopamine autoreceptors were needed for a maximum

inhibition by apomorphine of the accumulation of L-dopa in the striatum. Thus, 83% of the autoreceptors were thought to be spare receptors. If only a small percentage of dopaminergic receptors needed to be resynthesized for full rotational behavior to be observed, then this may explain why maximum rotational behavior returns earlier than the full return of the receptors as measured by radioligand binding techniques.

Another explanation for the faster recovery of rotational responses is that most radioreceptor assays measure a heterogeneous group of dopamine receptors. In addition to binding to the postsynaptic receptors which are involved in the rotational behavior, many radioligands also bind to dopamine receptors on the presynaptic nerve terminals of corticostriatal and nigrostriatal neurons [19], on serotonergic [13] and cholinergic [6] nerve terminals, and possibly on glial cells [12]. Thus, the turnover of dopamine receptors measured with radioreceptor binding techniques may represent the summation of multiple dopamine receptor subgroups each with different rates of receptor turnover.

As noted by others [21], pretreating mice with selective, reversibly acting dopaminergic antagonists to protect specific subtypes of dopamine receptors from irreversible inhibition may have many applications. For example, using this technique one may be able to study the function and turnover rates of each subtype of dopamine receptors. This paradigm may also be useful for isolating and identifying the different subtypes of dopamine receptors.

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