Abstract—Effect of lisuride, an ergot derivative of isolysergic structure, on dopamine-sensitive adenylate cyclase was studied in the homogenate of rat corpus striatum. Stimulatory action of lisuride, similar to the actions of dopamine and apomorphine, on striatal adenylate cyclase was potentiated significantly by guanosine triphosphate (GTP) and by guanyl-5'-yl imidodiphosphate (GMP-PNP), although with lisuride alone, there was only a slight stimulation. The maximal stimulation attained in the presence of GTP corresponded to about 1.4 times the basal rate of cyclic AMP formation in the homogenate and was abolished by an addition of haloperidol. Lisuride at a concentration above 3 μM inhibited stimulation of cyclic AMP formation by dopamine. The effect of lisuride and the extent of potentiation by the guanyl nucleotides were almost comparable to the effects of apomorphine, under corresponding conditions. Thus, lisuride, like apomorphine, acts as a partial agonist-antagonist, and has the ability to stimulate the dopamine-sensitive adenylate cyclase in the rat corpus striatum.

Drugs such as apomorphine stimulate dopaminergic receptors in the brain. Lisuride, a semi-synthetic ergot derivative of isolysergic structure (1), also exhibits potent dopaminergic actions in vivo, as demonstrated by enhancement of locomotor activity (2), induction of stereotyped behavior (2) and reduction in serum prolactin levels (3). Direct stimulatory action of lisuride on dopamine receptors of post synaptic membrane was suggested by the finding that the induction of stereotyped behavior was inhibited by haloperidol, a blocker of dopamine receptors, and not by α-methyl-p-tyrosine methyl ester, an inhibitor of dopamine synthesis (2). It was also reported that specific binding of 3H-spiroperidol and of 3H-lisuride was inhibited by lisuride (4) and (+)-butaclamol (5), respectively.

Adenylate cyclase in some regions of the brain is stimulated by dopamine in vitro (6–8), hence, the possibility that adenylate cyclase plays an important role in the post synaptic membrane has been discussed in relation to dopamine-dependent brain functions (9, 10). In fact, after solubilization of the synaptic membrane of bovine caudate nuclei, the enzyme activity of dopamine-sensitive adenylate cyclase could be reconstituted with two protein fractions, the one necessary for dopamine binding and the other for the catalytic site (11). Though less efficient than dopamine, apomorphine does stimulate the adenylate cyclase.

Abbreviations: GTP, guanosine triphosphate; GMP-PNP, guanyl-5'-yl imidodiphosphate; LSD, D-lysergic acid diethylamide; EGTA, ethylene glycol bis (β-aminoethyl ether)-N,N'-tetra-acetic acid.
activity of the rat striatal homogenate (7). Despite potent dopaminergic activities in vivo, however, dopaminergic ergots such as lisuride (12) and lergotrile (13, 14) are apparently devoid of stimulatory action on adenylate cyclase in striatal homogenates, although these ergots were found to inhibit dopamine-dependent stimulation of the enzyme. Based on these observations, it is generally assumed that stimulatory mechanisms of some ergots on the dopamine receptors may differ from that of apomorphine in which adenylate cyclase is involved (15).

Stimulation of adenylate cyclase by various substances appears to be variable, especially in the in vitro system and, in addition, it has been clarified that certain derivatives of the guanine nucleotide such as GTP act as a modulator to facilitate coupling between the two protein moieties in the adenylate cyclase-receptor complex (16-18).

This report describes a stimulatory effect of lisuride on dopamine-sensitive adenylate cyclase observed in the homogenate of rat corpus striatum under several conditions.

MATERIALS AND METHODS

**Materials:** [8-3H] cyclic AMP (30 Ci/mmol) was obtained from Radiochemical Centre, Amersham, England. All nucleotide derivatives, dopamine-HCl, phosphoenol pyruvate, EGTA and pyruvate kinase (Type II) were purchased from Sigma Chemical Co., U.S.A.. Lisuride hydrogen maleate, apomorphine-HCl and haloperidol were obtained from Schering AG, West Germany. All other substances were of analytical reagent grade and were purchased from Wako Chemical Co., Japan. Aqueous solutions of dopamine, apomorphine, haloperidol and lisuride were prepared daily for each experiment.

**Dissection of brain:** Male Sprague Dawley rats (300-450 g, fed *ad libitum*) were decapitated, the brain immediately removed and each region dissected on ice-cooled glass plates, as described by Glowinski & Iversen (19).

**Preparation of homogenates and assay for adenylate cyclase:** Preparation of homogenates and assay for adenylate cyclase activity were essentially the same as described by Kebabian et al. (8).

The standard assay mixture contained, in a final volume of 0.5 ml, 0.5 mM ATP, 10 mM theophylline, 2.0 mM MgCl₂, 0.2 mM EGTA, 80 mM Tris-maleate buffer pH 7.4 and an appropriate amount of the homogenate. When indicated, 50 μM GMP-PNP (Guanyl-5'-yl imidodiphosphate), 10 μM GTP, 4 mM phosphoenol pyruvate and 4 μg pyruvate kinase were also included in the mixture. The assay mixture was pre-incubated for 4 min at 30°C. The reaction was initiated by an addition of the homogenate and, after 3 min of incubation with constant shaking at 30°C, was terminated by placing the assay tube in a boiling water bath for 4 min. Under these reaction conditions, it was confirmed that cyclic AMP formation was proportional to the incubation time and to the protein concentration. Heat-denatured proteins were removed by centrifugation at 3,000 × g for 5 min and cyclic AMP concentration in the supernatant was determined by a protein-binding assay (20). The assay conditions were selected so that the method gave a linear calibration curve with authentic cyclic AMP from 0.5 to 3 pmoles. It was confirmed that lisuride and the guanyl
nucleotides did not disturb the cyclic AMP-binding assay. In each determination of the enzyme activity, dopamine and apomorphine were always used as reference substances in order to assure the activity of the homogenate preparation.

Protein concentration was determined according to the method of Lowry et al. (21), using bovine serum albumin as standard.

Statistical analysis: The one-way analysis of variance was applied and the means were compared according to method reported by Dunnett (22).

RESULTS

Dopamine-dependent adenylate cyclase in rat striatal homogenate: Dopamine in a concentration range from 0.1 to 50 μM enhanced the formation of cyclic AMP, and the half maximal effect was seen at 8 μM (Fig. 1). The stimulation reached a maximum with 50 μM dopamine. The mean basal rate (n=11) and the mean rate observed with 50 μM dopamine

![Fig. 1](image-url)  
**Fig. 1.** Effects of dopamine on basal activity of adenylate cyclase in rat striatal homogenate. The assay mixture contained, in a final volume of 0.5 ml, 0.5 mM ATP, 10 mM theophylline, 2.0 mM MgCl₂, 0.2 mM EGTA, 80 mM Tris-maleate buffer pH 7.4 and striatal homogenate (50–100 μg protein). Each value represents the mean ± S.E. in three experiments. Control value of cyclic AMP formation in the homogenate of this series was 133 ± 1 pmol cyclic AMP formed/min per mg of protein.
The stimulatory effect of dopamine was detected, to a lesser extent, also in the homogenate of the cerebral cortex, but not in homogenates prepared from the cerebellum, medulla oblongata and pons.

Apomorphine inhibited cyclic AMP formation with 50 μM dopamine, showing a half maximal effect at 4 μM (Fig. 2), as reported by others (8). In contrast to the inhibitory effect, however, a stimulatory effect of apomorphine on the adenylate cyclase activity was statistically insignificant; the rate of cyclic AMP formation with 10 μM apomorphine was 117.2 ± 5.3% of the basal activity (n=5) which is lower than the 141% reported by Kababian et al. (8) and the 124% by Schmidt and Hill (13). In the succeeding experiments with lisuride, the effects of 50 μM dopamine and of 10 μM apomorphine were measured as references in each striatal preparation to assure consistency of the experimental data.

Effect of lisuride on striatal adenylate cyclase activity: Effects of lisuride on the rate of cyclic AMP formation in the striatal homogenate were examined in the presence and absence of 50 μM dopamine, and the results obtained are shown in Fig. 3. Lisuride at a
concentration range from 3 to 10 μM induced only a slight increase in the rate of cyclic AMP formation in the absence of dopamine, but such was statistically insignificant (p>0.1). The dopamine-induced increase in the activity was inhibited in a dose-dependent manner with lisuride in a dose over 1 μM and the inhibitory effect at 100 μM was statistically significant. The extent of stimulation and inhibition was comparable to findings with 10 μM apomorphine in the same preparations.

Potentiation of the lisuride-dependent stimulation by guanyl nucleotides: As GMP-PNP (17) and GTP (16, 18) were recently reported to potentiate the stimulatory action of certain substances on adenylate cyclase in a cell free system, the stimulatory effects of lisuride and apomorphine on the striatal adenylate cyclase activity were examined in the presence of these guanyl nucleotides.

In the presence of GMP-PNP, a non-hydrolyzable analogue of GTP, the basal rate of cyclic AMP formation was increased by about 1.5 fold and the stimulatory effect of dopamine was slightly reduced (Table 1). Lisuride (Fig. 4), like apomorphine (Table 1), produced an increase in the rate of cyclic AMP formation, and though the percentage of the stimulation was small, the increments in the rate of cyclic AMP formation at 0.3 and 3 μM for lisuride

FIG. 3. Effects of lisuride on basal and dopamine-induced activities of adenylate cyclase in rat striatal homogenate. Effects of various concentrations of lisuride (○, ●) and 10 μM apomorphine (△, ▲) were measured in the presence (open symbols) and absence (closed symbols) of 50 μM dopamine under the conditions described for method. Each value represents the mean ± S.E. in six experiments. Basal rate of cyclic AMP formation in the homogenate of this series was 115±11 pmol cyclic AMP formed/min per mg of protein. * p<0.05.
TABLE 1. Stimulatory effect of dopamine and apomorphine on rat striatal adenylate cyclase in the presence of guanyl-5'-yl-imidodiphosphate (GMP-PNP) or GTP

| Guanyl nucleotide | Agent     | Conc. (μM) | cyclic AMP formation pmoles cAMP/min.mg | % of basal activity | % of control |
|-------------------|-----------|------------|----------------------------------------|---------------------|--------------|
| None              | Basal activity | 108±9     | 100                                    |                     |              |
|                   | Control   | —          | 174±0****                              | 161                 | 100          |
|                   | Dopamine  | 10         | 249±17**                               | 143                 |              |
|                   |           | 50         | 273±19**                               | 157                 |              |
|                   | Apomorphine | 1         | 195±17                                 | 112                 |              |
|                   |           | 3          | 226±12**                               | 129                 |              |
|                   |           | 10         | 230±15*                                | 132                 |              |
| 50 μM GMP-PNP     | Control   | —          | 92±7                                   | 86                  | 100          |
|                   | Dopamine  | 10         | 182±6***                               | 198                 |              |
|                   |           | 50         | 269±17***                              | 292                 |              |
|                   | Apomorphine | 1         | 119±8*                                 | 129                 |              |
|                   |           | 3          | 128±9*                                 | 139                 |              |
|                   |           | 10         | 126±11*                                | 137                 |              |

* Values are the mean ± S.E. of seven experiments.
** p<0.05, *** p<0.01, **** p<0.001 compared to control value in the presence of each guanyl nucleotides. 
*1. The assay mixture contained, besides components described for Fig. 1, 4 mM phosphoenol pyruvate, 4 μg of pyruvate kinase and 10 μM GTP.

Fig. 4. Effect of guanyl-5'-yl imidodiphosphate (GMP-PNP) on the lisuride-induced stimulation of adenylate cyclase activity. Stimulatory effects of various concentrations of lisuride (●) and of 10 μM apomorphine (▲) were measured in the presence of 50 μM GMP-PNP under the conditions described for Fig. 1. Each value represents the mean ± S.E. in seven experiments. Specific activity with 50 μM dopamine in the homogenate of this series was 230±10 pmol cyclic AMP formed/min per mg of protein. * p<0.05.
and at 3 and 10 μM for apomorphine were statistically significant.

In contrast to GMP-PNP which enhances the basal rate, GTP produced an insignificant reduction in the basal rate of cyclic AMP formation. When expressed in terms of percent-stimulation, the stimulatory effect of dopamine in the presence of 10 μM GTP was 292%. It should be, however, noted that the absolute rate of cyclic AMP formation observed in the presence of 50 μM dopamine was much the same in the presence of GTP and of GMP-PNP (Table 1).

The stimulatory effects of lisuride and of apomorphine were markedly potentiated and the maximal stimulations observable at 3 or 10 μM were near or over 140% of the basal rate, respectively (Fig. 5 and Table 1).

At concentrations over 10 μM, there was an inhibitory component of the lisuride action on adenylate cyclase.

Inhibition of the lisuride-induced stimulation by haloperidol: The effect of haloperidol, a blocker of dopaminergic receptor, on the stimulations of adenylate cyclase activity by
Dopamine, apomorphine, and lisuride were then examined in the presence of 10 μM GTP. As seen in Fig. 6, the stimulatory effects of lisuride (3, 10 μM), dopamine (50 nM) and apomorphine (10 μM) on striatal adenylate cyclase were all but abolished by 10 μM haloperidol.

**FIG. 6.** Antagonistic effect of haloperidol on the lisuride-, apomorphine- and dopamine-induced stimulation of striatal adenylate cyclase in the presence of GTP. Effects of 3 and 10 μM lisuride, 10 μM apomorphine and 50 μM dopamine were examined in the presence (lined column) and absence (blank column) of 10 μM haloperidol. The assay mixture contained 10 μM GTP as described for Figure 5. Each value was given as the mean ± S.E. in four experiments. Statistical significance against the basal value were ∗ p<0.05; ∗∗ p<0.01 and against the corresponding value without haloperidol ∗∗∗ p<0.05; ∗∗∗∗ p<0.01.

**DISCUSSION**

It is generally accepted that the adenylate cyclase system in a number of peripheral tissues consists of, at least, three distinct components, i.e. a catalytic unit, a hormonal receptor site and a guanine nucleotide regulatory component (23). The essential role of GTP for a stimulatory mechanism of dopamine on caudate adenylate cyclase was also seen with the purification and reconstitution of adenylate cyclase in the caudate nucleus (11, 24). In the present study, we observed that GTP and GMP-PNP potentiated the stimulatory action of dopamine on adenylate cyclase of rat striatal homogenate and that the latter nucleotide also produced a significant increase in the basal rate of cyclic AMP formation in the homogenate lacking dopamine. These observations are in agreement with those reported by Roufogalis et al. (16), although implications of the increased basal activity by GMP-PNP are obscure.

Stimulatory activities of lisuride and apomorphine on striatal adenylate cyclase observed with and without the guanyl nucleotides were considerably low as compared to those of dopamine, apomorphine, and lisuride were then examined in the presence of 10 μM GTP.

As seen in Fig. 6, the stimulatory effects of lisuride (3, 10 μM), dopamine (50 μM) and apomorphine (10 μM) on striatal adenylate cyclase were all but abolished by 10 μM haloperidol.
dopamine. Apomorphine does mimic to a lesser extent, the effect of dopamine and, at same
time acts as a dopamine agonist on adenylate cyclase in striatal homogenate (6, 15). This
type of agonist is designated as a partial agonist (15) or a mixed agonist-antagonist. A
slight stimulation by lisuride of cyclic AMP formation, the potentiation by GTP and GMP-
PNP and inhibition by lisuride of dopamine-dependent cyclic AMP formation were detected
in the homogenate of the rat corpus striatum. The extent of these responses was comparable
to findings with apomorphine in the same homogenate preparations. In addition, the
stimulation by lisuride and apomorphine were abolished by haloperidol. Therefore, lisuride,
like apomorphine, probably acts as a partial agonist on dopamine receptors linked to
adenylate cyclase.

The stimulatory activities of ergot derivatives on dopamine-sensitive adenylate cyclase
in tissue homogenates revealed discrepancies. LSD, ergometrine and ergocristine, which
have potent dopaminergic actions in vivo, stimulate the activity of adenylate cyclase in cell-
free preparations of the rat striatum (13, 25–27). Conversely, lergotrile introduced as a
dopaminergic agonist was later reported not to stimulate the enzyme in the striatal homo-
genate (13, 14). Other ergots such as ergonovine, ergocristine and elymoclavine slightly
stimulate the striatal enzyme (13, 17), whereas only LSD and ergometrine out of 8 ergot
derivatives including lisuride and bromocriptine exhibited weak stimulant properties (23).
This latter observation is coincident with the result by Pieri et al. (12), who noted the lack of
stimulatory effects of lisuride, but differs from the findings by Pagnini et al. (28), who detected
a bromocriptine-dependent increase in the rate of cyclic AMP formation in the rat striatal
homogenate.

However, all experiments cited above were carried out using striatal homogenates
without supplements of the guanyl nucleotides. Like the results obtained in the present
study for lisuride and apomorphine, Fuxe et al. (17) observed that a slight stimulation of
striatal adenylate cyclase by various ergot derivatives such as lergotrile and bromocriptine
were potentiated by a supplement of GMP-PNP in striatal homogenates. Therefore, the
potentiation of the ergot-dependent stimulation by the guanyl nucleotides can be taken as
evidence indicating, at least, potential abilities of these ergot drugs in stimulating some of
the dopamine receptors linked to adenylate cyclase. It may also be inferred that some
fundamental subunits necessary for the coupling of dopamine receptor to adenylate cyclase
are impaired and cannot be activated effectively by partial agonists upon cell disruption.
In this regard, lisuride and bromocriptine produced increases in cyclic AMP formation in
striatal slices, and such was prevented by fulphenazine, a blocker for dopamine receptors
(23, 29).

Though the stimulatory potency of lisuride on adenylate cyclase seems to be clarified,
the possibility that active metabolites and not lisuride itself might be responsible for the
dopaminergic actions of lisuride in vivo was suggested by Pieri et al. (12). These workers
found no stimulatory effect of lisuride in striatal homogenates. In this connection, Toda
and Oshino (30) prepared six kinds of the major metabolites including demethyl-, deethyl-
and hydroxylated- lisurides by using a perfused rat liver system. Central dopaminergic
effects of these metabolites were examined in our laboratory by measuring induction of contra-lateral rotation in uni-laterally denervated rats with 6-hydroxydopamine, and no activity was detected in any of these metabolites (Hara & Ikoma, unpublished observations). Keller and Prada (31) reported that when rats were given proadifen (SKF-525A), an inhibitor of microsomal drug metabolizing system, there was a potentiation and prolongation of the action of lisuride in vivo. Therefore, lisuride is the only active ingredient responsible for the central dopaminergic activities induced by lisuride administration in vivo.

Synaptic dopaminergic receptors can be classified into two types; those associated with adenylate cyclase (D-1 receptor) and those unrelated to this enzyme (D-2 receptor) (15). Using this classification, Kebabian and Calne (15) reported that dopaminergic ergot-agonists are considered to act on the D-2 receptor as potent agonists and on D-1 receptor as potent antagonists with weak agonist properties. Thus, the pharmacological significance of the lisuride-induced cyclic AMP formation in striatal homogenate remains to be explored in intact animals.

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