Pharmacology Biochemistry & Behavior, Vol. 34, pp. 355–360. © Pergamon Press plc, 1989. Printed in the U.S.A. 0091-3057/89 $3.00 + .00

Effect of YM-09151-2, a Putative D_2 Dopamine Receptor Antagonist, on Dopamine Metabolism in the Striatum of Rats

SHINJI SHIBANOKI, TAIZO KUBO, YOSHIKO IMAMURA, SATOSHI ASAI, YUTAKA ISHII, KOJI TADA* AND KOICHI ISHIKAWA[1]

*Departments of Pharmacology and *Neuropsychiatry, Nihon University School of Medicine, Itabashi, Tokyo 173, Japan*

Received 20 October 1988

SHIBANOKI, S., T. KUBO, Y. IMAMURA, S. ASAI, Y. ISHII, K. TADA AND K. ISHIKAWA. *Effect of YM-09151-2, a putative D_2 dopamine receptor antagonist, on dopamine metabolism in the striatum of rats.* PHARMACOL BIOCHEM BEHAV **34**(2) 355–360, 1989.—YM-09151-2, a novel benzamide derivative, significantly increased the concentrations of dopamine (DA) metabolites, both 3,4-dihydroxyphenylacetic acid and 3-methoxy-4-hydroxyphenylacetic acid (homovanillic acid). The maximum increase in such metabolites was about 4-fold the concentration in control animals, and was observed at 2 hr after oral administration. 3-Methoxy-4-hydroxyphenylethylene glycol, a metabolite of noradrenaline, was slightly increased in its concentration exhibiting a transient effect, but 5-hydroxyindoleacetic acid was not. YM-09151-2 antagonized the decreasing effects of apomorphine, a nonselective DA agonist, and LY-171555, a selective D_2 DA receptor agonist, on the concentrations of DA metabolites in the brain. In contrast, SCH-23390, a selective D_1 DA receptor antagonist, did not antagonize the effects of DA agonist. These results strongly suggest that YM-09151-2 is a selective antagonist of D_2 DA receptor and a candidate as a new antipsychotic agent for clinical use.

YM-09151-2 Monoamine metabolism D_2 antagonist Rats Brain

NEUROLEPTICS constitute a group of drugs which are used for the treatment of psychotic disorders in clinical institutes. This group of drugs is classified into many derivatives based on their chemical structures including phenothiazines, butyrophenones and thioxanthenes. The mode of action common to these agents is a blocking effect on dopamine (DA) receptors, and this is suspected to underlie their antipsychotic action. Central DA receptors consist of two subtypes, D_1 and D_2 receptors, which are classified according to ligands of different selectivity and with different effect on adenylate cyclase activities (5). It has been shown that the intensity of the blocking action of D_2 receptor is significantly correlated to the antipsychotic efficacy (4,20).

cis-N-(1-benzyl-2-methylpyrrolidin-3-yl)-5-chloro-2-methoxy-4-methyl-aminobenzamide (YM-09151-2) is one of the benzamide derivatives whose antipsychotic potential has been suggested by behavioral pharmacological studies (15,26). Its blocking effect on DA receptors has also been demonstrated (7, 14, 18). Recent results of more detailed binding assays (12, 16, 24) and electrophysiological investigations have emphasized that YM-09151-2 acts as a blocking agent of D_2 rather than D_1 DA receptors (27,28).

Recent advances in the study of DA receptors have revealed their localization in the nerve cells of the central nervous system, especially of the nigro-striatal pathway (1,5). According to workers in this field, it has been confirmed that presynaptic D_2 DA receptors control the release and synthesis of DA at the nerve terminals (8, 19, 29). D_1 receptors, on the other hand, exist in the postsynaptic membrane, couple with adenylate cyclase which is closely related to the second messenger, and control the activity of this enzyme (5,21). This indicates that the drugs acting on D_1 and D_2 receptors may exhibit different biochemical effects on monoamine metabolism. In the present study, therefore, we examined the effect of YM-09151-2 on the intracerebral monoamine metabolism and its action mechanism by comparing those of other agents which influence the DA metabolism by acting on DA receptors.

METHOD

Animals

Male Wistar rats, each weighing about 200 g, were used throughout the experiments. They were obtained from Shizuoka

[1]Requests for reprints should be addressed to Koichi Ishikawa, M.D., Ph.D., Department of Pharmacology, Nihon University School of Medicine, 30 Oyaguchi-Kami Machi, Itabashi, Tokyo 173, Japan.

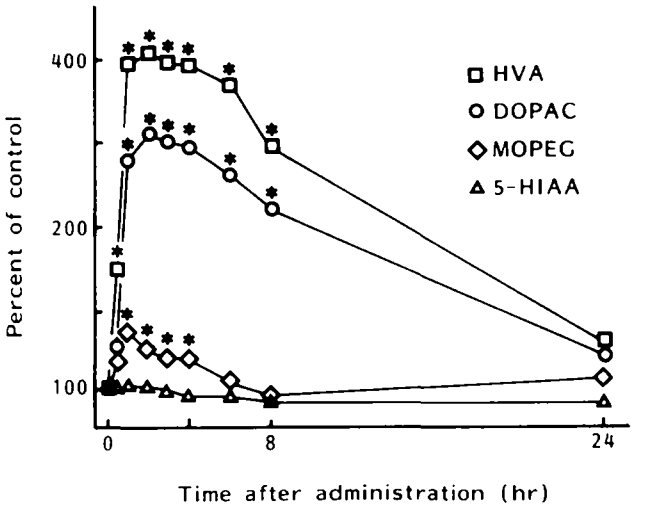

FIG. 1. Time course of changes in concentrations of monoamine metabolites in the striatum of rats. The animals were administered orally with 10 mg/kg of YM-09151-2 and sacrificed at different times after the administration. The monoamine metabolites DOPAC (control level, 2076 ± 387 ng/g wet tissue), HVA (1678 ± 298), MOPEG (213 ± 65) and 5-HIAA (543 ± 102) were determined by high performance liquid chromatography with electrochemical detection. Each point and bar represent the mean ± S.D. for 6 animals. *Significantly different from the control, which was administered with distilled water ($p<0.01$).

Experimental Animal Colony (Hamamatsu, Japan), and housed for at least 1 week prior to the experiments in a room where the temperature (23 ± 0.5°C), humidity (60 ± 5%) and light cycle (12-hr illumination with the light turned on at 7:00 a.m.) were controlled. During this period, the rats received standard food and water ad lib.

Chemicals

YM-09151-2 was a generous donation from Yamanouchi Pharmaceuticals (Tokyo, Japan). SCH-23390 and LY-171555 were also donations from Schering-Plough Corporation (Bloomfield, NJ) and Eli Lilly (Indianapolis, IN), respectively. Apomorphine and haloperidol were commercially obtained from Sigma (St. Louis, MO). Authentic standards for monoamine-related substances, including noradrenaline (NA), dopamine (DA), 5-hydroxytryptamine (5-HT), 3-methoxy-4-hydroxyphenylethylene glycol (MOPEG), 3,4-dihydroxyphenylacetic acid (DOPAC), 3-methoxy-4-hydroxyphenylacetic acid (homovanillic acid; HVA) and 5-hydroxyindoleacetic acid (5-HIAA), were all purchased from Sigma. Internal standard substances, isoproterenol (for the assay of monoamines and MOPEG) and 3,4-dihydroxyphenylpropionic acid (for the assay of acidic metabolites) were obtained from Sigma and ICN Pharmaceuticals (Plainview, NY), respectively. Reagent grade chemicals for extraction and chromatography were all purchased from a single commercial source (Wako Pure Chemicals, Osaka, Japan) and used without further purification.

Drug Administration and Sample Preparation

YM-09151-2 was administered orally to the animals at dose levels of 0.1, 0.3, 1, 3 and 10 mg/kg. Haloperidol was also given orally at the same dose levels. These drugs were suspended in 1% carboxymethyl cellulose solution at the time of administration, and were introduced into the animals using a gastric needle at a volume of 0.05 ml/100 g. The control animals received the same volume of solvent only. The animals were sacrificed at 2 hr after the administration.

The effects of DA receptor antagonists on the DA metabolism induced by the DA agonists, apomorphine and LY-171555, were examined. In this series of experiments, the agonist was injected intravenously into animals at 1 hr prior to intravenous injection of the antagonist. The animals were sacrificed at 30 min after injection of the antagonist.

The animals were sacrificed by microwave irradiation (5 kW, for 1.2 sec). The brain was removed as quickly as possible and placed on an ice-cold glass plate. The brain was dissected into 7 regions including the striatum, midbrain and pons-medulla oblongata according to the procedures of Glowinski and Iversen (6). The brain samples were stored in a deep freeze (− 80°C) until assay of monoamine-related substances.

Determination of Monoamine-Related Substances

The intracerebral concentrations of monoamines and metabolites were analyzed quantitatively according to the procedures described previously (10). To each brain tissue sample stored in the deep freeze, weighing about 100 mg, was added 250 μl of 0.025 N HCl containing internal standards. The mixture was homogenized and extracted with 3 ml of n-butanol. Then, 5 ml of n-heptane and 200 μl of 0.1 N HCl were added to 2.5 ml of the butanol extract, and the mixture was shaken vigorously and allowed stand to form layers. The aqueous layer was used for the analysis of precursor amino acids and monoamine transmitters, while 6.5 ml of the fluid from the organic layer was, together with 100 μl of Tris-HCl buffer, vibrated and its aqueous layer used for the analysis of acidic metabolites. For the separation and determination of these substances, a high performance liquid chromatograph (Model 510, Waters Association, Milford, MA) with a reversed phase packed column (Ultrasphere-ODS; average particle size, 5 μm; 250 × 4.5 mm inside diameter; Altex Scientific, Berkeley, CA), six port injector (Model 7125, Rheodyne, Berkeley, CA) and an electrochemical detector (EC-100, Eicom, Kyoto, Japan) with a glassy carbon electrode were used. As the mobile phase, 0.1 M sodium citrate/citric acid buffer (pH 4.5) containing 1% of tetrahydrofuran was employed for the separation of monoamines and MOPEG, and 0.075 M sodium citrate/citric acid buffer (pH 3.5) containing 1% of tetrahydrofuran, 12% of acetic acid and 10% of methanol, for the separation of acidic metabolites. Applied voltages were set at 650 and 800 mV for the assay of monoamines and MOPEG, and acidic metabolites, respectively.

RESULTS

The time course of the changes in concentrations of monoamine-related substances was observed in the striatum after a single oral dosage (10 mg/kg) of YM-09151-2. No significant changes in the concentrations of the monoamine transmitters themselves (NA, DA and 5-HT) were observed, in comparison with those of the control animals which received the solvent, at any time after administration of the drug. On the other hand, the concentrations of the DA metabolites, DOPAC and HVA, began to increase significantly at 30 min after the administration (Fig. 1). A peak was reached at 2 hr after the administration and the increase was 4 times as high as that in the control group.The increases in both DOPAC and HVA were restored to the concentrations in the control at 24 hr after the administration.

MOPEG, a metabolite of NA, was also increased significantly at 1 hr after oral administration of YM-09151-2. However, the increase was 1.5 times as high as that in the control and recovered 6 hr after the administration, showing that the drug exerted a

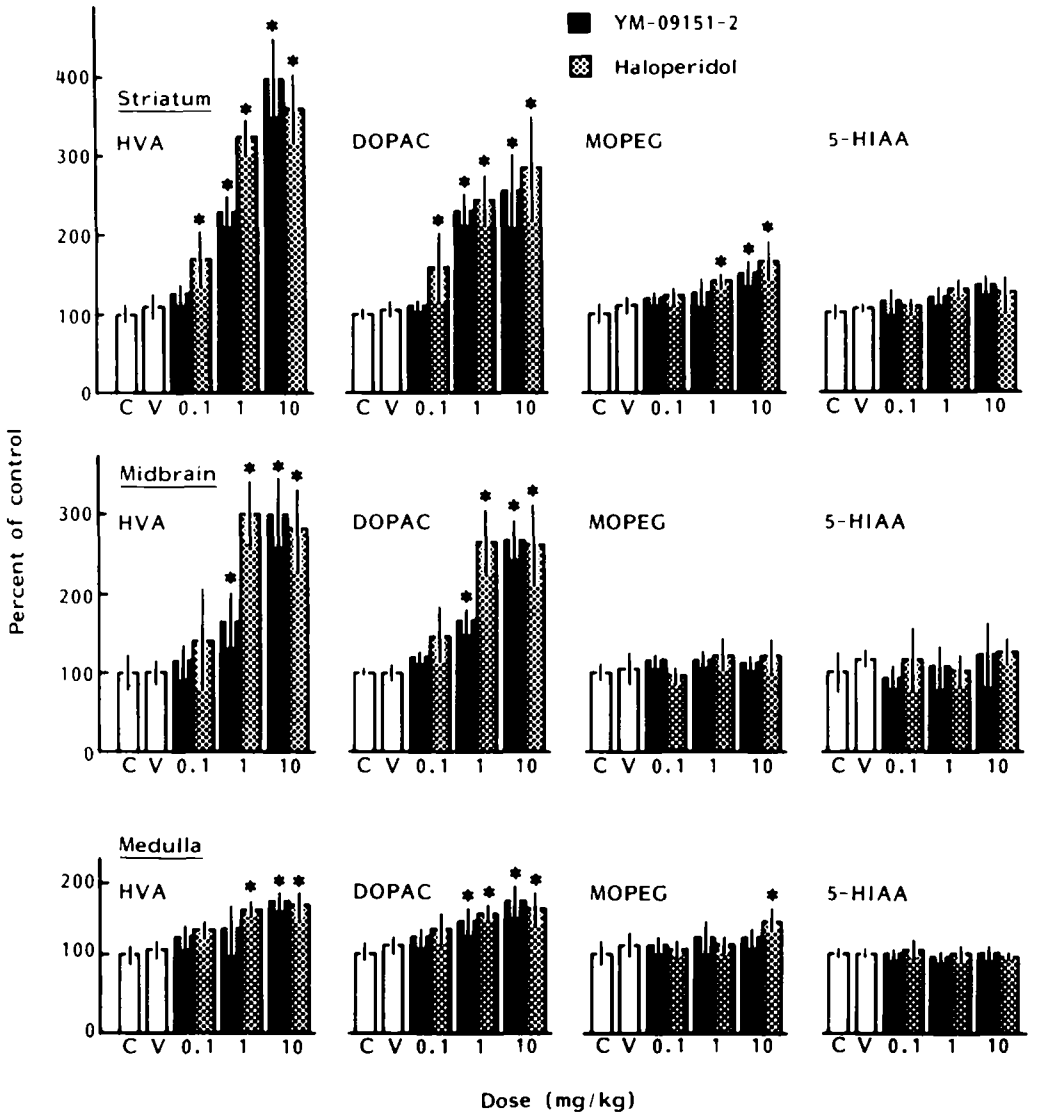

FIG. 2. Effects of YM-09151-2 and haloperidol on the concentrations of monoamine metabolites in the striatum and medulla oblongata of rats. Both drugs were injected in the dose range for 0.1 to 10 mg/kg into the animals which were sacrificed at 2 hr after the administration. Each point and bar represent the mean ± S.D. for 6 animals. *Significantly different from the group injected with vehicle (V) ($p<0.01$).

weaker and more transient effect on the adrenergic than the dopaminergic system. In the case of the serotonergic marker, 5-HIAA, no significant changes in concentration occurred at any time after the administration of YM-09151-2.

Measurements were also carried out on other parts of the brain, yielding similar results to those for the striatum. Irrespective of the activity level of the dopaminergic system, the administration of YM-09151-2 caused increases in the DOPAC and HVA levels which remained for 4 to 8 hr. The concentration of MOPEG also increased but that of 5-HIAA did not, even in the midbrain where the serotonergic system is active (see Fig. 2).

Figure 2 shows changes in the levels of monoamine metabolites in the dissected brain regions following oral administration of different doses of YM-09151-2 and haloperidol. When the dose was as low as 0.1 mg/kg, haloperidol increased both the DOPAC and HVA levels in the striatum, but YM-09151-2 caused no significant changes in the concentrations of these metabolites. In a case where 1 mg/kg of drug was injected, both YM-09151-2 and haloperidol increased significantly the concentration of HVA with a significant difference in the rate between these drugs. The maximum effect was observed at a dose level of 10 mg/kg for both drugs. In the striatum, haloperidol also increased the level of MOPEG from a dose of 1 mg/kg and YM-09151-2 did at a dose of 10 mg/kg. Neither YM-09151-2 nor haloperidol increased significantly the concentration of 5-HIAA.

Both HVA and DOPAC were also observed to be dose-dependently increased by the oral administration of the drugs in the midbrain (Fig. 2). No significant change was, on the other hand, observed in the concentrations of MOPEG and 5-HIAA in this region. In pons-medulla oblongata, comparatively high doses of YM-09151-2 and haloperidol increased the levels of HVA and DOPAC, but did not of MOPEG and 5-HIAA. When the compar-

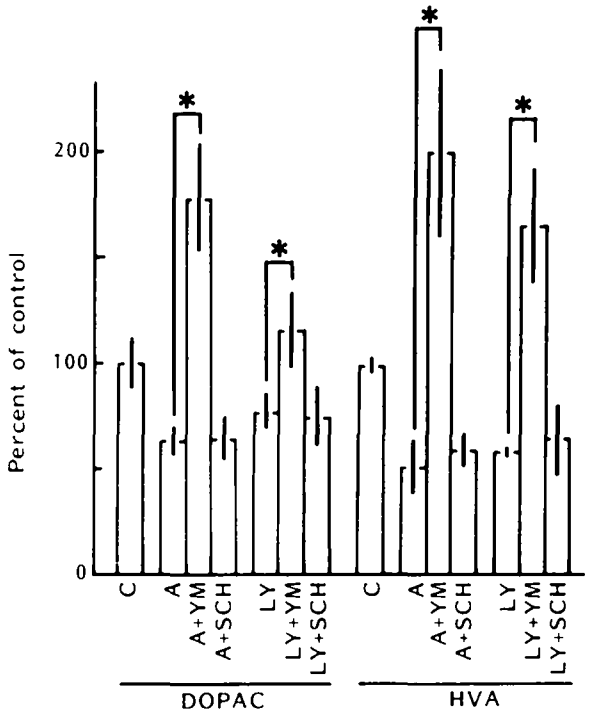

FIG. 3. Effects of YM-09151-2 and SCH-23390 on the metabolism of DA induced by DA agonists in the striatum of rats. The DA antagonist (YM-09151-2 or SCH-23390) was injected intravenously at 1 hr prior to intravenous injection of the agonist (apomorphine or LY-171555). The animals were sacrificed at 1 hr after the injection of agonist. Each column and bar represent the mean ± S.D. for 6 animals. All groups treated with drugs were significantly different from the control (C). *Significant difference was observed between the groups ($p<0.01$).

ison was carried out for the concentrations of HVA, the rate was greater in the striatum in comparison with medulla. The same result was obtained for DOPAC. Therefore, the increasing rates of DA metabolites depended on activity of the dopaminergic system.

When the animals were sacrificed at 2 hr after the oral administration of 0.1 mg/kg of YM-09151-2, the DOPAC and HVA levels in the striatum revealed no significant differences. When the same amount of haloperidol was administered orally, the DA metabolites increased slightly. When the agents were given intravenously, however, even 0.01 mg/kg of YM-09151-2 or haloperidol could significantly increase the DOPAC and HVA levels in the striatum (Table 1). When the changes in metabolite levels were compared between the oral administration of 0.1 mg/kg and the intravenous administration of 0.01 mg/kg, the ratio was 3.8 for YM-09151-2 and 2.0 for haloperidol. This indicates that haloperidol, rather than YM-09151-2, tends to be effective even if given orally.

Significant decreases in the striatal levels of DOPAC and HVA were induced when apomorphine, a nonselective DA agonist, and LY-171555, a selective D_2 receptor agonist, where injected intravenously (Fig. 3). Intravenous pretreatment with 0.01 mg/kg of YM-09151-2 offset such decreases by the agonists, and both DOPAC and HVA were even higher than in the control. However, pretreatment with 1 mg/kg of SCH-23390 failed to counteract the decreases caused by apomorphine and LY-171555, and the metabolite levels were lower than in the control.

With the aim of comparing the effects of DA antagonists on the tyrosine hydroxylase (TH) activity in vivo, measurements were made of the accumulated DOPA, a precursor amino acid to DA produced by NSD-1015 treatment (Fig. 4). YM-09151-2 administration had no effect at a dose level of 0.001 mg/kg but increased the DOPA accumulation at 0.01 mg/kg. An augmentative effect was also noted with haloperidol, but it required a 10 times larger dose than with YM-09151-2, i.e., 0.1 mg/kg, to induce an increase in the DOPA accumulation. When 0.1 mg/kg was administered, haloperidol increased the accumulation by nearly 2 times compared to the control, whereas YM-09151-2 did so by 2.6 times. This was the dose of YM-09151-2 producing the maximum increase in the DOPA accumulation; haloperidol could further increase the accumulation dose-dependently until a plateau was reached at 1 mg/kg, with a maximum change rate of 2.6 times.

DISCUSSION

The present study was carried out to examine the effect of

TABLE 1

COMPARISON OF THE EFFECTS OF YM-09151-2 AND HALOPERIDOL ACCORDING TO DIFFERENT ROUTES OF ADMINISTRATION

Drug	Dose (mg/kg)	Route	Concentration (ng/g wet tissue) DOPAC	HVA
Control	—	—	996 ± 60	659 ± 78
YM-09151-2	0.1	PO	1039 ± 60	786 ± 68
	0.01	IV	3815 ± 351	2783 ± 249
Haloperidol	0.1	PO	1539 ± 375	1071 ± 205
	0.01	IV	3020 ± 348	2371 ± 289

Each value represents the mean ± S.D. for 6 animals.

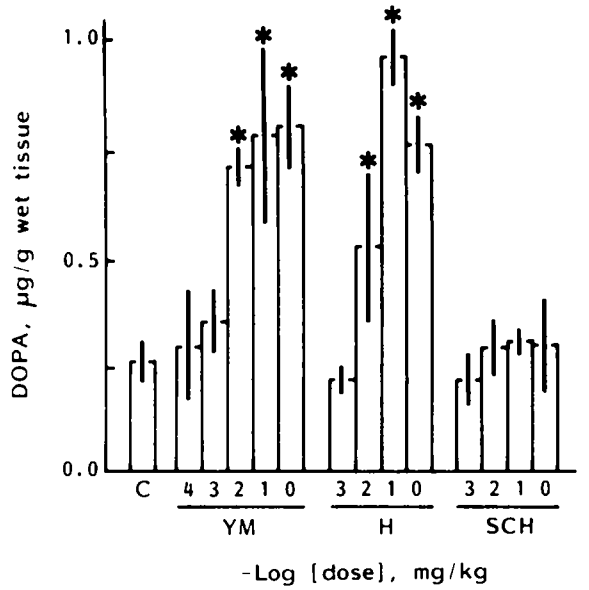

FIG. 4. Effects of YM-09151-2, haloperidol and SCH-23390 on the accumulation of DOPAC in the striatum of rats. The DA antagonist (YM-09151-2, haloperidol or SCH-23390) was injected intravenously at 1 hr prior to intravenous injection of NSD-1015 (an inhibitor of DOPA decarboxylase). The DOPA accumulation was determined at 30 min after the injection of NSD-1015. Each column and bar represent the mean ± S.D. for 6 determinations. *Significantly different from the control ($p<0.01$).

YM-09151-2, a novel benzamide derivative, on the metabolism of monoamine transmitters, especially of dopamine, in the brain of rats. Previous behavioral pharmacological experiments (15,26) and receptor binding assays (11, 12, 16, 24) have indicated that YM-09151-2 acts as an antagonist of DA receptor. Classification of DA receptors has now revealed the existence of two subtypes, D_1 and D_2, according to the effects on the adenylate cyclase activity (5,21). Benzamide derivative, of which the typical drug is sulpride, has a blocking effect on D_2 DA receptor and has been proven to be clinically effective for the treatment of psychotic disorders (23). D_2 receptors are located in DA-containing neurons on both pre- and postsynaptic sites in the brain (5,21). Of these two subtypes, the presynaptic D_2 receptors are considered to function as autoreceptors, controlling the synthesis and release of the transmitter DA at the dopaminergic nerve terminals (8, 19, 29). It is speculated therefore that an agent affecting the D_2 receptors also exerts a substantial effect on the DA metabolism.

D_2 receptors are not uniformly distributed in the brain. The intracerebral regional distribution is thought to coincide with the distribution of the dopaminergic innervation (1, 13, 17). In the present experiments, YM-09151-2 dose-dependently increased the levels of DA metabolites, DOPAC and HVA. The degree of its incremental effect, however, differed greatly among the regions evaluated. The striatum was the region in which the effect of YM-09151-2 was most strongly observed. On the other hand, little effect was evident in medulla-oblongata. These results agreed with the previously reported intracerebral distribution of D_2 receptors (13,17). Similar regional differences in action were also observed with haloperidol.

For the same drug, the oral effect is debilitated in comparison with the intravenous effect because the oral effect is influenced by pharmacokinetic factors including the absorption process. The difference between the effects obtained by intravenous and oral administrations is defined as the bioavailability, which is a term used to express the extent to which a drug reaches its site of action or a biological fluid from which the drug has access to its site of action (2). The decrease in effects on monoamine metabolites due to the difference in routes of administration was greater in the case of YM-09151-2 than in the case of haloperidol. Because this comparison can be interpreted as reflecting the difference in bioavailability, YM-09151-2 had a lower bioavailability than haloperidol. However, when the maximum effect was compared between the two drugs, YM-09151-2 was found to have a greater effect than haloperidol. This suggests that YM-09151-2 is greater in its efficacy and may be more selective in its effect on the D_2 DA receptor than haloperidol.

Apomorphine is a nonselective agonist for DA receptors, while LY-171555 is a selective agonist for D_2 receptors (25). The DA metabolites, DOPAC and HVA, were significantly decreased by the administration of these agonists. It seems quite possible that, if D_2 receptors were autoreceptors, administration of their agonist would cause a decrease in the release of DA and a consequent decrease in its metabolites. It follows, on the other hand, that administration of their antagonist would enhance the DA release, elevating the DOPAC and HVA levels. It has been established that, on the basis of its effect on the adenylate cyclase activity and of the results of receptor binding assays, SCH-23390 is a selective antagonist of D_1 receptors (9). Pretreatment with SCH-23390 failed to show the above-mentioned reduction in intracerebral DA metabolites caused by apomorphine or LY-171555. This is not surprising because these receptors are not sensitive to this agent. Pretreatment with YM-09151-2, on the other hand, not only counteracted the decrease in metabolites but also increased their levels even in relation to the control levels. It may be concluded therefore that YM-09151-2 acts on neurons at different sites from those affected by SCH-23390 and that, of the two kinds of receptors, YM-09151-2 acts on the D_2 receptors.

TH is the rate limiting enzyme in catecholamine synthesis and converts tyrosine into DOPA. Measurements of the accumulated DOPA after a certain treatment will thus reflect the TH activity, which is controlled, at least partially, by autoreceptors. NSD-1015 is an inhibitor of DOPA decarboxylase, so that administration of this agent readily allows determinations to be made of the DOPA levels (3). It was found that YM09151-2 administration induced DOPA accumulation, which indicated a rise in TH activity. A similar effect was noted with haloperidol, which blocks, though not selectively, D_2 receptors. Such an effect was absent from SCH-23390, which is a selective antagonist of D_1 receptors. These findings suggest that the antagonistic effect on D_2 receptors relieves the inhibition of DA synthesis by the autoreceptors, activating the rate-limiting enzyme TH and enhancing DA synthesis. In this mechanism, D_1 receptors apparently have no role to play.

YM-09151-2 was found to increase the NA metabolite, MOPEG, temporarily. Many previous reports have demonstrated that neuroleptics including phenothiazines and butyrophenones not only block the dopaminergic but also the adrenergic system (22). It is reasonable to consider that YM-09151-2 may also act on the adrenergic system to some extent. However, its effect does not appear to be sufficiently great to warrant clinical attention. In contrast, there was no sign of YM-09151-2 exerting an influence on the serotonergic system like phenothiazines and butyrophenones.

From the results obtained in the present biochemical experiments, it may be concluded that YM-09151-2 is a selective blocking agent of D_2 receptors. This agrees with the experimental finding that the electrophysiological change caused by D_2 agonist was completely recovered by YM-09151-2 (27). It also agrees with the results of receptor binding assays (16,24). While the weaker effect of orally given YM-09151-2 than of haloperidol may reflect

the difference in bioavailability between these two agents, the efficacy of YM-09151-2 is considered to be comparable to haloperidol.

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