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Effects of tetrahydroprotoberberines on dopamine receptor subtypes in brain[1]

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Abstract The effects of 12 tetrahydroprotoberberines (THPBs) on D_1 and D_2 receptors labelled with [^{3}H]DA, [^{3}H]Sch-23390 and [^{3}H] spiperone were evaluated. Their effects on the activity of adenylate cyclase stimulated with DA 40 μmol/L were also assessed.

All of the *l*-THPBs tested behaved as DA receptor antagonists with preferential affinity toward the D_1 receptors. Among them, *l*-stepholidine (*l*-SPD), a THPB analog with 2 hydroxy groups at the C_2 and C_{10} positions, was the most potent. Its affinity toward D_1 receptors was 4-7 times higher than that toward D_2 receptors. The results suggest that the hydroxy groups in *l*-THPBs are very important factors in determining the affinity to DA receptors. Moreover, *d*-tetrahydropalmatine (*d*-THP), a dextro-THPB analog, displayed no affinity for the D_2 receptor subtype, while its optical isomer, *l*-THP, was a DA receptor antagonist. This indicates that the levo-optical configuration is necessary for the affinity of THPBs to DA receptors. In addition, *l*-SPD was 18 times more potent than haloperidol with respect to binding to D_1 receptors, but 14 times weaker for D_2 receptors. Thus, it is expected that the clinical effects of *l*-SPD can be distinguished from that of haloperidol.

Key words adenyl cyclase; dopamine receptors; [^{3}H]Sch-23390; [^{3}H]spiperone; *l*-stepholidine; *l*-tetrahydropalmatine; *d*-tetrahydropalmatine; tetrahydroprotoberberines

Although many tetrahydroprotoberberines (THPBs) have been isolated or synthesized, there have been very few systematic pharmacological studies, except our early works[1] which indicated that *l*-tetrahydropalmatine (*l*-THP) is a potent sedative-tranquilizing agent having few side effects. Among the THPBs, *l*-THP is the first one to become a drug and is included in various Chinese textbooks of pharmacology as well as in the Chinese Pharmacopoeia[2]. Recently, we have further demonstrated that *l*-THPBs, including *l*-THP, are a new class of dopamine (DA) receptor antagonists[3,4]. *l*-Stepholidine (*l*-SPD) was the most potent analog. Furthermore, *l*-SPD has been used successfully in the treatment of patients with brain DA dysfunction or migraine. These clinical results[5] have prompted an active study of the neuropharmacological actions of THPBs. This paper reports on the actions of THPBs on 2 DA receptor subtypes: D_1 and D_2.

Materials

Tetrahydroberberine (THB), mp 162-5℃, 2,3-dihydroxy-9,10-dimethoxy-THPB (I) and 2,3,9,10-tetrahydroxy-THPB (II) were synthesized in our Institute. *d*-Tetrahydropalmatine (*d*-THP), mp 141-2℃, $[\alpha]_D^{15}+289.5$; *l*-THP, mp 141-2℃, $[\alpha]_D^{15}-288$. *l*-Stepholidine (*l*-SPD), mp 161-2℃, $[\alpha]_D-400$; *l*-scoulerine, mp 204℃, $[\alpha]_D^{20}-124$; *l*-corydalmine, mp 172-3℃, $[\alpha]_D-337.4$; *l*-xylopinine, mp 181-2℃, $[\alpha]_D^{15}-277.2$; *l*-iso-corypalmine, mp 241-2℃, $[\alpha]_D-314.3$; corypalmine, mp 215-7℃ and *l*-discretamine, mp 212℃, $[\alpha]_D-235.7$ were isolated from *Stephania*[6] (Tab 1). They

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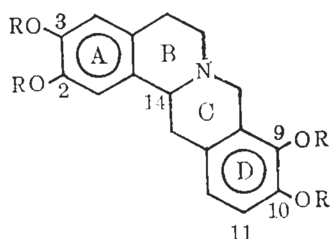
were dissolved in a small amount of 1% lactic acid by heating, adjusted with NaOH 0.1 mol/L to pH 3.5–5.5 and then diluted with 1% ascorbic acid to the needed concentrations. The kits for radioimmunoassay (RIA) of cyclic adenosine monophosphate (cAMP) were purchased from the Shanghai Second Medical University. [^{3}H] Spiperone 1.1 TBq/mmol, [7,8–^{3}H]DA 1.8 TBq/mmol, and [^{3}H]Sch–23390 3.3 TBq/mmol were purchased from the Radiochemical Centre Amersham (U K).



Tab 1. **Chemical structures of tetrahydroprotoberberines (THPBs).**

Compound	R position 2	3	9	10	11
Tetrahydroberberine (THB)	$-CH_2-$		CH_3	CH_3	H
THPB–I	H	H	CH_3	CH_3	H
THPB–II	H	H	H	H	H
l–Stepholidine (*l*–SPD)	H	CH_3	CH_3	H	H
l–Scoulerine	H	CH_3	H	CH_3	H
l–Discretamine	CH_3	H	CH_3	H	H
l–Corydalmine	CH_3	CH_3	CH_3	H	H
l–Iso-corypalmine	H	CH_3	CH_3	CH_3	H
Corypalmine	CH_3	H	CH_3	CH_3	H
l–Tetrahydropalmatine (*l*–THP)	CH_3	CH_3	CH_3	CH_3	H
l–Xylopinine	CH_3	CH_3	H	CH_3	OCH_3

Methods and results

Competition of THPBs for [^{3}H]spiperone binding to D_2 receptors The experiments were performed as previously described[3]. Twelve tested THPBs inhibited [^{3}H]spiperone binding to D_2 receptors with different potencies (Tab 2). Among them, *l*-SPD showed the highest potency although it was still 14 times weaker than haloperidol, a potent D_2 antagonist. The structure-activity relationship between THPBs and D_2 receptors can be summarized as follows: 1) THPBs with two OH groups were more potent than those with only one OH group. For example, *l*–SPD and *l*–scoulerine were more potent than *l*–iso–corypalmine, corypalmine and *l*–corydalmine. 2) The 2 OH groups should be attached to the A and D rings, respectively. If they are attached to the same ring, their inhibitory effects on the D_2 receptor are reduced. For instance, THPB–I was weaker than *l*–SPD and *l*–scoulerine. 3) Analogs with 2 OH groups located on C_2 and C_{10} (*l*–SPD) or on C_2 and C_9 (*l*–scoulerine) were more potent than those with 2 OH groups on C_3 and C_{10} (*l*–discretamine). It appears that the C_2 position is critically related to the affinities of THPBs for D_2 receptors. 4) The effects of THPBs are dramatically decreased (>90%) when the OH groups are substituted by methoxy or methylenedioxy groups, as in *l*–THP and THB. 5) With a methoxy group located on C_{11}, the affinity of THPB, such as *l*–xylopinine, towards D_2 receptors was also decreased. It was over

Tab 2. **Relative potency of THPBs in inhibition of [^{3}H]spiperone binding to D_2 receptors on striatum membranes from calf.**

Compound	K_I(μmol/L)	Ratio
Haloperidol	0.006	1
Clozapine	4.4	733.4
l–Stepholidine	0.085	14.2
l–Scoulerine	0.18	30.0
l–Discretamine	0.6	100.0
l–Iso-corypalmine	1	166.7
Corypalmine	0.55	91.7
l–Corydalmine	0.65	108.3
THPB–I	0.6	100.0
THPB–II	0.75	125.0
Tetrahydroberberine	0.75	125.0
l–Tetrahydropalmatine	0.85	141.7
l–Xylopinine	7.5	1250.0
d–Tetrahydropalmatine (*d*–THP)	>100	>16666.7

10 times weaker than *l*-THP. 6) The absolute configurations of THPB are very important for DA receptor binding. While *l*-THP had some affinity for D_2 receptors, its optical isomer, *d*-THP, had hardly any, indicating that the position of the hydrogen atom attached to the chiral carbon (C_{14}) has a decisive influence on THPB affinity towards D_2 receptors.

Competition of THPBs for [^{3}H]DA binding to D_1 receptors with high affinity state

1 Preparation of calf striatal membranes[7] The striata were dissected from the brain within 1 h after the calf was killed. The tissue was homogenized in 50 volumes (wt/vol) of ice-cold TENA buffer (Tris-HCl 50 mmol/L, EDTA-Na_2 5 mmol/L, nialamide 12.5 μmol/L, ascorbic acid 1.1 mmol/L, pH 7.4), and centrifugated at 20 000 × g, (2℃, 10 min). The precipitate was suspended and recentrifugated through over and again. The final pellet was resuspended in TENA buffer and kept in a freezer (−25℃). The frozen homogenate could be stored for one month with no deterioration of DA receptor binding.

2 Competitive binding to D_1 receptors with high affinity state. Before each experiment, the frozen homogenate was thawed and diluted with ice-cold TENA buffer to 14 mg/ml. Each test tube contained 7 mg wet tissue (0.5 ml) and various tested drugs. The concentrations of [^{3}H]DA were 0.1 to 6.7 nmol/L. Apomorphine 1 μmol/L was used as a cold ligand to define non-specific binding. The total reaction volume was 0.6 ml. Binding was performed in an ice bath with duplicate tubes and each experiment was repeated 3 times. After all tubes were vortexed, they were incubated in a water bath (30℃) for 30 min. The reaction was terminated by transferring the tubes to an ice-bath. The reaction mixture was rapidly filtered under a vacuum through GF/B filters and rinsed 3 times with 5 ml ice-cold Tris-HCl buffer to remove the free radioligands. The filters were dried at 80℃ for 20 min and their radioactivities were determined with a liquid scintillation spectrometer (YSJ-78, China) at an efficiency of 60%.

[^{3}H]DA bound to calf striatal membranes in a saturable manner with high affinity. Scatchard and Hill analyses[8] indicated the presence of a homogenous binding sites over the range of [^{3}H]DA concentrations used. The number of binding sites (B_{max}) was 11.6 pmol/g wet tissue and the dissociation constant (K_D) was 2.7 nmol/L. The Hill number (n_H) was 1.05.

In competitive binding tests, [^{3}H]DA 1.3 nmol/L and 5 concentrations (1-10 000 nmol/L) of tested drugs were used. The inhibition constants (K_i) were estimated according to a method descibed in the literature[8]. The results showed that 2 DA receptor agonists, DA and apomorphine, exhibited high affinities at the D_1 receptors (Tab 3). The affinity of *l*-SPD for D_1 receptors was slightly more potent than that of DA and apomorphine. On the other hand, the affinity of haloperidol, a potent D_2 receptor antagonist, was only one-eighteenth of that of *l*-SPD. On the contrary, haloperidol was even less potent than those THPBs without an OH group, such as *l*-THP and THB. Thus, it is clear that

Tab 3. Relative potency of THPBs in inhibition of [^{3}H]DA binding to high affinity state of D_1 receptors on calf striatum membranes.

Compound	K_1(nmol/L)	Ratio
Dopamine	25	1.2
Apomorphine	33	1.6
Haloperidol	380	18
l-Stepholidine	21	1
l-Scoulerine	29	1.4
l-Iso-corypalmine	73	3.5
l-Corydalmine	80	3.8
Corydalmine	290	13.8
l-Tetrahydropalmatine	180	8.6
Tetrahydroberberine	290	13.8

THPBs have higher a affinity for D_1 receptors than butyrophenone.

Competition among THPBs for [^{3}H] Sch-23390 binding to D_1 receptors

1 Preparation of calf striatal membranes[9] The dissected striata from calf brains were homogentized in 50 volumes (wt/vol) ice-cold Tris-HCl buffer 50 mmol/L (pH 7.4) and centrifuged at 20 000 × g for 10 min (4℃). The pellet was resuspended in ice-cold Tris-HCl buffer and centrifuged again. The final pellet was resuspended in imidazol buffer, 16.67 mmol/L (pH 7.4), containing (theophylline 16.67, EGTA 1 and $MgSO_4$ 1 mmol/L). The homogenate could be kept in a freezer (−25℃) for 3 wk.

2 Competitive binding to D_1 receptors The frozen homogenate was thawed and diluted with imidazol buffer to 20 mg/ml wet tissue. The range of [^{3}H]Sch-23390 concentration was from 0.1 to 6.2 nmol/L and *cis*-flupenthixol 4 μmol/L was used as a cold ligand. The total reaction volume was 0.5 ml. All tubes were incubated at 37℃ for 15 min in a water bath. The reaction was terminated as in the case of [^{3}H]DA binding except that the filters were washed with ice-cold 0.9% NaCl 15 ml. The radioactivity was measured with a liquid scintillation spectrometer.

With Scatchard and Hill analysis, the B_{max} of [^{3}H]Sch-23390 bound to calf striatal membranes was estimated to be 13.5 pmol/g wet tissue and the K_D was 1.0 nmol/L. The n_H was 1.06, indicating binding of [^{3}H]Sch 23390 to sites with a single affinity (Fig 1).

In competition for [^{3}H]Sch-23390 binding, 0.34 nmol/L or 0.63 nmol/L of [^{3}H]Sch-23390 and 1-1000 nmol/L of tested drugs were used. The K_i of drugs were estimated as previously described[8]. The results showed that Sch-23390 and *cis*-flupenthixol, both D_1 receptor antagonists, exhibited the highest potency with K_i, 0.84 and 3.1 nmol/L, respectively (Tab 4). The affinities of THPBs with 2 OH groups, such as *l*-SPD and *l*-scoulerine, were higher than those without an OH group, such as THB and *l*-THP. Therefore, OH groups attaching to rings A and D appear to be beneficial to THPBs with respect to binding to D_1 receptors. Sulpiride, a selective D_2

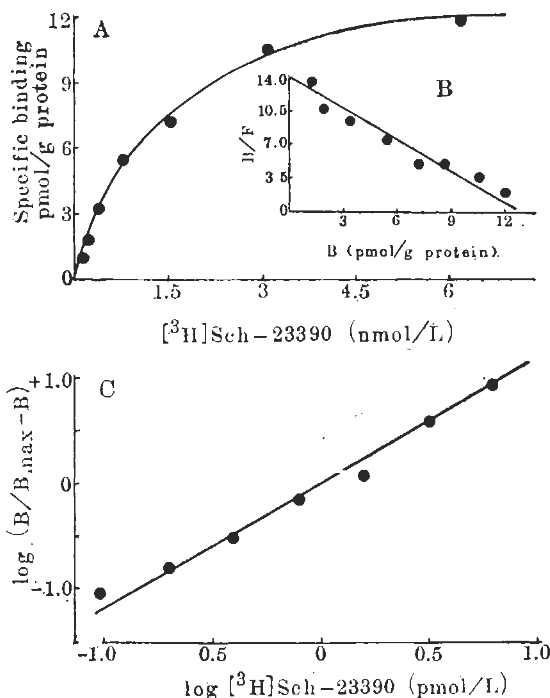


Fig 1. Binding of [^{3}H]Sch-23390 to D_1 sites on membranes from rat striatum. A) Specific binding of [^{3}H]Sch-23390; B) Scatchard plots, B/F (pmol/g × nmol/L); C) Hill plots.

Tab 4. Relative potency of selective D_1 receptor antagonists and THPBs in inhibition of [^{3}H] Sch-23390 binding to D_1 receptors on calf striatum membranes.

Compound	K_i(nmol/L)	Ratio
Sch-23390	0.84	1
cis-Flupentixol	3.1	3.7
l-Stepholidine	13	15.5
l-Scoulerine	42	50.0
Tetrahydroberberine	330	392.9
l-Tetrahydropalmatine	1100	1309.5
Sulpiride	>10 000 (no effect)	>11 904.8

receptor antagonist, had no effect on [^{3}H] Sch-23390 binding to D_1 receptors, even at 10 μmol/L.

Effects of THPB on cAMP level stimulated by DA

1 Preparation of brain membranes and measurement of drug actions[10] Fresh striata were dissected from the brains of male rats (Kunming species, 200 ± SD 12 g) killed by decapitation. The tissue was homogenized in 20 volumes (wt/vol) of ice-cold Tris-HCl buffer 50 mmol/L, pH 7.7 (containing EGTA 2 mmol/L). The homogenate was centrifuged at 1000 × *g* for 10 min (4℃) and the supernatant was diluted with ice-cold Krebs-Ringer buffer and centrifuged at 20 000 × *g* for 15 min at 4℃. The final pellet was resuspended in Tris-HCl buffer at 50 mmol/L (containing EGTA 2, theophylline 10, $MgSO_4$ 2 mmol/L) and the tissue concentration was equivalent to 1 mg/ml of wet weight (wt/vol). Fifty μl of DA (final concentration 40 μmol/L), different concentrations of test drugs (50 μl) and ATP (final concentration 0.5 mmol/L) were added to 200 μl of the tissue suspension and vortexed. Basal adenylate cyclase activity was determined in the absence of DA and tested drugs. The reaction was initiated with ATP and carried out in a shaking water bath (30℃) for 2.5 min. The reaction was terminated by transferring the tubes into a boiling water bath for 2 min. The reaction mixture was centrifuged for 10 min at 1000 × *g* (4℃). An aliquot of the supernatant (250 μl) was taken out and dried under reduced pressure at room temperature (20-25℃ for about 4 h). The level of cAMP was determined in triplicate assays.

2 Measurement of cAMP by radioimmunoassay[11] The adequate acetic acid buffer (pH 4.75) was added to the dried sample tubes to dissolve the white crystals. The titre of anti-cAMP serum was 1:20 000 with a sensitivity of 0.01 pmol. A standard curve was made in each experiment with cAMP 0.2-2 pmol/10-100 μl. The total volume of the reactive solution was 304 μl. After all sample tubes were vortexed, they were incubated at 4℃ for 20 h. The reactive solution was rapidly filtered under a vacuum (25 lbs) over microporous filter paper (25 mm diameter, 0.45 μ). The filters were then rinsed rapidly with 10 ml of ice-cold phosphate buffer (pH 6), dried at 80℃ for 20 min and inserted into liquid scintillation vials containing 5 ml of scintillation liquid (xylene, PPO and POPOP). Radioactivity trapped on the filters was counted using a liquid scintillation spectrometer The values of cAMP were estimated from the standard curve. The IC_{50} of drug (concentration caused 50% reduction) against the DA stimulated cAMP formation was estimated graphically. Each drug tested was examined 3 to 4 times independently.

The data in Tab 5 show that *cis*-flupenthixol, a selective D_1 receptor antagonist, inhibited the activity of adenylate cyclase with an IC_{50} of 1.0 μmol/L. Since THB, *l*-THP and *l*-SPD shared similar inhibitory activities, it is suggested that THPB can block the D_1 receptor subtype, although their effects were less potent than those of *cis*-flupenthixol. The effect of *l*-SPD was approximately 3 times more potent than that of chlopromazine indicating that *l*-SPD may be more potent than the phenothiazines. Sulpiride, a D_2 receptor

Tab 5. Effects of THPBs and DA receptor antagonists on adenylate cyclase activity stimulated with DA (40 μmol/L) in homogenates of rat striatum.

Compounds	IC_{50}(μmol/L)
cis-Flupenthixol	1.0
l-Stepholidine	2.0
Chlopromazine	5.5
Tetrahydroberberine	9.0
l-Tetrahydropalmatine	13
Sulpiride	>100

antagonist, displayed hardly an inhibitory effect on adenylate cyclase activity.

Discussion

Based on the results of biochemical [3,12], behavioral[4,13], and electrophysiological experiments, it has been suggested that *l*-THPBs are a new type of DA receptor antagonists. Sch-23390 and spiperone are used as a tool to distinguish drug actions on D_1 and D_2 receptor subtypes. In this paper, the results showed that *l*-THPBs inhibited [^{3}H]Sch-23390 and [^{3}H] spiperone binding to D_1 and D_2 receptors, suggesting that *l*-THPBs are mixed DA receptor antagonists. It is worth noting that the *l*-THPBs are more potent at the D_1 receptors, and that the affinity of *l*-SPD for D_1 receptors (Tab 3 and 4) was about 4-7 times more potent than that for D_2 receptors (Tab 2). In addition, *l*-SPD was 18 times more potent than haloperidol on D_1 receptors; but 14 times weaker on D_2 receptors (Tab 2 and 3). The notion that *l*-THPBs are D_1 receptor antagonists is supported biochemically since they inhibited DA-stimulated adenylate cyclase activity.

The structure-activity studies of *l*-THPBs displayed the critical role of the OH groups on C_2, C_3, C_9 and C_{10}. The order of affinity of *l*-THPBs to DA receptors is as follows: with 2 OH groups > with 1 OH group > none. The hydroxy group on C_2 is particularly important for high potency as in the case of *l*-SPD. Why is *l*-SPD the most potent analog among the *l*-THPBs? The data from X-ray diffraction and quantum chemical calculations have provided a partial answer[14]. The presence of 2 OH groups in *l*-SPD increases the electron density and raises the torsional angle between the A and D rings, resulting in enhancement of the pharmacological potency. It has been deduced that the OH group on C_2 can readily form a hydrogen bond with the residual groups on DA receptors and helps *l*-SPD bind firmly to DA receptors. Moreover, the results from X-ray diffraction have defined that both the N atom and H bond at the chiral carbon (C_{14}) in the *l*-THPBs molecules just make an opposite direction. This means that the N atom is oriented downward *vs* the horizontal plane of the D ring, while the H bond is oriented upward *vs* the plane. Such a common stereostructure is considered to be a requirement for stereospecificity for *l*-THPBs to DA receptors. However, the absolute configuration of *d*-THP become a stereo-hindrance and interferes with *d*-THP binding to DA receptors.

We have found *l*-SPD to exhibit an agonistic property only in rotational behaviour of rats lesioned with 6-OH-DA[13]. Such an action has never been found in any other DA receptor antagonist before. How can this be explained? One possibility is that *l*-SPD, like apomorphine and DA (Tab 3), displays good potency toward the high affinity state of D_1 receptors, which represents the DA agonist binding sites with poor affinity for DA antagonists[15]. The second possibility is that the denervation supersensitivity would change the responsive nature of D_1 or/and D_2 receptor subtypes to *l*-SPD. This problem is now being tackled.

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四氢原小檗碱同类物对 D_1 和 D_2 多巴胺受体亚型的作用

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摘要　应用放射配体受体结合试验，评价四氢原小檗碱同类物(THPB)对脑内 DA 受体亚型的亲和力.试验证明,*l*-THPB 对 [^{3}H]spiperone 和 [^{3}H]Sch-23390 均有拮抗性抑制，表明分别与 D_1 和 D_2 两受体亚型均有亲和力，为确定 *l*-THPB 为 DA 受体阻滞剂提供直接证据；其中作用最强者为 C_2 和 C_{10} 位有羟基的左旋千金藤立定 (*l*-SPD)，它对 D_1 的亲和力比对 D_2 约强 4-7 倍. [^{3}H]DA 是 D_1 受体亚型的高亲和态的配体，D_1 激动剂与它有较好的亲和力，*l*-SPD 含有 DA 的结构要素，对它的亲和力略比 DA 和去水吗啡两激动剂强,可能为 *l*-SPD 兼有激动作用的旋转试验提供依据.

应用 DA 40 μmol/L 刺激腺苷酸环化酶活力，由放射免疫法测定所增加的 cAMP 含量，选择性 D_1 阻滞剂三氟噻吨(*cis*-fluopenthixal)能拮抗这种作用. 试验证实多种 *l*-THPB 也有相似作用，表明 *l*-THPB 确有 D_1 受体亚型阻滞剂的作用特性.

关键词　腺苷酸环化酶；　多巴胺受体；　[^{3}H]Sch-23390；　[^{3}H]螺哌隆；　左旋千金藤立定；　左旋四氢巴马汀；　右旋四氢巴马汀；　四氢原小檗碱