

Comparison of 12-chloroscoulerine enantiomers on animal behavior to dopamine receptors¹

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KEY WORDS 12-chloroscoulerine; *l*-stepholidine; apomorphine; dopamine D₁ receptors; Sch23390; radioligand assay; stereotyping; catalepsy; locomotion

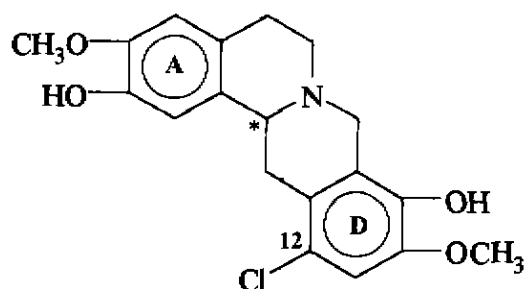
ABSTRACT

AIM: To compare the pharmacological characteristics of 12-chloroscoulerine (CSL) enantiomers to dopamine (DA) receptors. **METHODS:** Radioligand receptor binding assay with calf striatum and behavioral tests of mice or rats were used. **RESULTS:** In the competitive binding assay, the affinities (K_i) of *l*-CSL to D₁ and D₂ receptors were 5.7 nmol·L⁻¹, while those of *d*-CSL for D₁ and D₂ receptors were 135 and 9150 nmol·L⁻¹, respectively. The K_i of *dl*-CSL to D₁ and D₂ receptors were 8.9 and 9.6 nmol·L⁻¹, respectively, which were slightly weaker than that of *l*-CSL. In the behavioral experiments, CSL enantiomers 5-60 mg·kg⁻¹ antagonized the stereotypy induced by apomorphine in rats, and 5-150 mg·kg⁻¹ produced catalepsy. The enantiomers 10-60 mg·kg⁻¹ reduced the mice jumping behavior induced by amphetamine + levodopa. *l*-CSL 10-80 mg·kg⁻¹ antagonized the spontaneous locomotor activity of normal or amphetamine-treated mice. **CONCLUSION:** CSL enantiomers are antagonists to DA receptors; *l*-CSL > *dl*-CSL >> *d*-CSL.

INTRODUCTION

dl-12-Chloroscoulerine (*dl*-CSL), a potent

analog of tetrahydroprotoberberines (THPB), shares an isoquinoline structure with two OH groups at C₂ and C₉ and chlorine at C₁₂ position. *d*-CSL has the potent affinities to dopamine (DA) D₁ and D₂ receptors^[1]. Its activities are similar to that of *l*-stepholidine (SPD)^[2-5], a leading compound of THPB. SPD shows DA receptors antagonistic action in the behavioral studies on stereotypy and catalepsy, but it displays the DA agonist action on the contralateral rotation in the 6-OHDA-lesioned rats^[5-6]. Thus *dl*-CSL has also the dual action on DA receptors and it is very similar to SPD^[7-10]. *l*-Tetrahydropalmatine (*l*-THP), another analog of THPB, is a DA receptor antagonist, while the *d*-THP enantiomer is a prototype of DA depletor^[8,9]. Based on the differential actions of THP enantiomers to DA receptors, it is suggested that the *l*-CSL enantiomer should be a more potent DA receptor antagonist or/and agonist than *d*-CSL enantiomer. The present study aimed at the comparative study of CSL enantiomers to DA receptors.



Chemical structure of CSL enantiomers

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MATERIALS AND METHODS

Drugs and reagents SPD (mp 163°C, $[\alpha]_D$ -440° in pyridine) was isolated from *Stephania intermedia* LO; *dl*-CSL, *l*-CSL (mp 161-162°C, $[\alpha]_D^{11.5}$ -223.19°, CHCl₃, C 0.14), *d*-CSL (mp 161

-162 °C, $[\alpha]_D^{25} + 222.53^\circ$) were synthesized in Shanghai Institute of Materia Medica. [^3H]Sch23390 (3071 GBq nmol \cdot L $^{-1}$, Radiochemical Center, Amersham), [^3H]spiperone (592 GBq nmol \cdot L $^{-1}$, radiochemical centre, Amersham); Sch23390 (RBI), *d*-amphetamine (Amp, BDH), levodopa (Sigma), haloperidol (Hal, Haipu Pharmaceutic Factory, Shanghai, China), apomorphine hydrochloride (Shenyang First Pharmaceutic Factory, China), and clozapine (Clo, Shanghai Pharmaceutic Factory, China) were used.

Animals Sprague-Dawley (SD) rats (δ , 210 g \pm s 42 g) and Kun Ming species mice (δ , 19 g \pm 2.6 g, Grade II, Shanghai Experimental Animal Center, China, Certification No 005 by Animal Management Committee, Chinese Academy of Sciences) were used.

Receptor binding assay Calf striatal membrane protein was prepared as previous report^[1]. [^3H]Sch 23390 and [^3H]spiperone were used for binding assay respectively to D₁ and D₂ receptors^[10-11]. The K_d values of D₁ and D₂ receptors were 1.65 and 0.48 nmol \cdot L $^{-1}$, the receptors densities (B_{\max}) were 907.8 and 125.7 pmol \cdot L $^{-1}$ /g protein, respectively, and Hill number (n_H) were 0.91 and 0.99^[1], respectively.

Rat stereotypy Rats were placed in the observing cages for 20 min before drug treatment to adapt to a new environment. After ip apomorphine (Apo) 5 mg \cdot kg $^{-1}$ 3-5 min, the stereotypy induced by Apo was observed, and CSL enantiomers were given (ip) 15 min after Apo. The 4-grade scoring system^[12] for gnawing, licking, rearing, sniffing and vigorous movements without purpose were scored. The effect of CSL enantiomers was assessed by the antagonism to Apo-induced stereotypy.

Rat catalepsy^[13] The catalepsy of rats was measured as followed; rats' front paws were put on wood cylinder 9 cm high, and hind paws on the ground. The time of its still posture remained after drug was recorded as the catalepsy criteria scored.

Jumping behavior in mice The jumping behavior in mice was elicited by amphetamine (Amp, ip) 10 mg \cdot kg $^{-1}$ + levodopa (ip) 200 mg \cdot kg $^{-1}$ 15 min after the injection. The mice started to jump almost immediately following levodopa injection. Tested

compounds such as *l*-CSL, *d*-CSL, Hal, Clozapine (Clo) were given (ip) 5 min before Amp respectively. The effects of the compounds were evaluated by a "jumping medium number"^[14] of mice.

Spontaneous locomotor activity of mice^[15]

Every group of 9 mice was tested for separately 3 times in the photocell boxes. Amphetamine (Amp, ip) 10 mg \cdot kg $^{-1}$ was injected by followed *l*-CSL, or Clo with 5 min apart, the spontaneous motor activity of grouped mice was recorded automatically on the basis of light beam interrupted by mice during a 5-min period. The drug tested groups and control group were compared parallelly.

RESULTS

Affinities of CSL enantiomers Results showed that CSL enantiomers had the different affinities to dopamine D₁ and D₂ receptors. The affinity of *l*-CSL was the most potent one among CSL enantiomers. The K_i value of *l*-CSL was at 5.7 nmol \cdot L $^{-1}$ (Tab 1) to both dopamine D₁ and D₂ receptors, which were 24 and 1605 times stronger than that of *d*-CSL to D₁ and D₂ receptors respectively. The K_i values of *dl*-CSL was 8.9 and 9.6 nmol \cdot L $^{-1}$ to D₁ and D₂ receptors, respectively. And the D₂ activity was more active than that of *l*-SPD, of which D₁ activity was similar to that of *dl*-CSL. The potency order was *l*-CSL > *dl*-CSL > > *d*-CSL (Tab 1).

Tab 1. Affinities of CSL enantiomers to dopamine receptors.

CSL enantiomers	K_i /nmol \cdot L $^{-1}$	
	D ₁	D ₂
Sch23390	0.28	-
Haloperidol	-	0.14
<i>l</i> -SPD	8.6	80
<i>l</i> -CSL	5.7	5.7
<i>dl</i> -CSL	8.9	9.6
<i>d</i> -CSL	135	9150

CSL enantiomers antagonized APO-induced stereotyped behavior The stereotypy in rats induced by Apo 5 mg \cdot kg $^{-1}$ was markedly reduced after ip injection of CSL enantiomers 5-60 mg \cdot kg $^{-1}$. The effect of *l*-CSL was the most potent one among CSL

enantiomers. At the dose of *l*-CSL 5–40 mg·kg⁻¹, the stereotypy was obviously reduced ($P < 0.01$) or abolished in a dose-dependent manner. Although *d*-CSL 40–60 mg·kg⁻¹ also reduced stereotypy, but its antagonistic action was equal to that of *l*-CSL 5 mg·kg⁻¹. Thus, the potency of *l*-CSL was about 12 times more potent than that of *d*-CSL (Tab 2).

Tab 2. Blockaded effect of CSL enantiomers on Apomorphine-induced stereotyped behavior rats ($n = 6$), $\bar{x} \pm s$. ^a $P > 0.05$, ^b $P < 0.05$, ^c $P < 0.01$ vs Apo.

Drugs	Dose/mg·kg ⁻¹	Score
Apo 5		3.0 ± 0.6
Apo 5 + NS		3.3 ± 0.5 ^a
Apo 5		3.5 ± 0.6
Apo 5 + Hal 1		0 ^c
Apo 5		3.6 ± 0.5
Apo 5 + <i>l</i> -CSL 5		1.6 ± 1.5 ^c
Apo 5		2.8 ± 0.4
Apo 5 + <i>l</i> -CSL 10		1.3 ± 0.8 ^b
Apo 5		3.2 ± 0.4
Apo 5 + <i>l</i> -CSL 20		0.5 ± 0.5 ^c
Apo 5		3.6 ± 0.5
Apo 5 + <i>l</i> -CSL 40		0 ^c
Apo 5		3.5 ± 0.6
Apo 5 + <i>dl</i> CSL 20		1.5 ± 1.1 ^c
Apo 5		3.0 ± 0.6
Apo 5 + <i>dl</i> CSL 40		0.8 ± 0.7 ^c
Apo 5		3.5 ± 0.8
Apo 5 + <i>d</i> CSL 40		1.8 ± 1.0 ^c
Apo 5		3.3 ± 0.8
Apo 5 + <i>d</i> CSL 60		1.5 ± 1.4 ^c

CSL enantiomers evoked catalepsy in rats

The results showed that normal saline (NS) group did not display any cataleptic effect, while haloperidol (Hal) had very profound cataleptic effect at the 1 mg·kg⁻¹ and lasted for a long time (455 ± 37 min). However, *l*-CSL exhibited its cataleptic effect with a dose-dependent manner at the range of 5–80 mg·kg⁻¹, but it was far weaker against Hal. The cataleptic effect of *dl*-CSL enantiomer was slightly weaker than the same doses of *l*-CSL enantiomer. And the cataleptic effect of *d*-CSL at the 150 mg·kg⁻¹ was also weaker than that of *l*-CSL 5 mg·kg⁻¹ (Tab 3).

CSL enantiomers blocked mice jumping behavior induced by amphetamine plus levodopa Mice in saline group did not show any

Tab 3. CSL enantiomers evoked catalepsy in rats. $n = 6$, $\bar{x} \pm s$.

Drugs	Dose/mg·kg ⁻¹	Time of appearance catalepsy/min	Retaining time of catalepsy/min	Score
NS		–	–	0
Hal	1	9.5 ± 1.2	455 ± 37	5.0 ± 0.0
<i>l</i> -CSL	5	4.1 ± 2.3	8.0 ± 5.9	2.7 ± 1.6
<i>l</i> -CSL	10	3.8 ± 1.8	12.8 ± 4.7	3.6 ± 0.5
<i>l</i> -CSL	20	2.9 ± 2.1	18.2 ± 7.1	4.2 ± 0.8
<i>l</i> -CSL	40	3.0 ± 1.5	22.2 ± 7.9	4.6 ± 0.8
<i>l</i> -CSL	80	2.5 ± 1.0	46 ± 10	5.0 ± 0.0
<i>dl</i> -CSL	5	5.7 ± 2.2	3.0 ± 3.0	1.6 ± 1.4
<i>dl</i> -CSL	10	10.5 ± 3.5	8.0 ± 4.0	3.3 ± 1.8
<i>d</i> -CSL	150	12.6 ± 1.6	3.1 ± 2.8	1.6 ± 1.0

jumping. When the mice were ip Amp 10 mg·kg⁻¹ + levodopa 200 mg·kg⁻¹, the jumping was revealed vigorously with 340 times in one hour. This jumping behavior was profoundly reduced or abolished by Hal 1 mg·kg⁻¹ and Clo 5 mg·kg⁻¹ (Tab 4). The jumping behavior was also reduced by *l*-CSL at the dose range of 10–60 mg·kg⁻¹ and *d*-CSL 40 mg·kg⁻¹, and the jumping numbers were reduced from 340 times in one hour of control to 151–67 times and 121 times respectively. These results indicate that *l*-CSL and *d*-CSL have antagonistic action on DA receptors.

Tab 4. Effect of CSL on *l*-dopa induced jumping behavior in Amp-treated mice. $n = 9–14$.

Drugs	Dose/mg·kg ⁻¹	Jumping/No·h ⁻¹
Amp 10 + <i>l</i> -dopa	200	340 (198–409)
Amp 10 + <i>l</i> -dopa + Hal	1	0 (0–8)
Amp 10 + <i>l</i> -dopa + Clo	2.5	124 (3–432)
Amp 10 + <i>l</i> -dopa + Clo	5	0 (0–63)
Amp 10 + <i>l</i> -dopa + <i>l</i> -CSL	10	151 (45–405)
Amp 10 + <i>l</i> -dopa + <i>l</i> -CSL	30	135 (16–324)
Amp 10 + <i>l</i> -dopa + <i>l</i> -CSL	60	67 (0–226)
Amp 10 + <i>l</i> -dopa + <i>d</i> -CSL	40	121 (34–382)

Inhibition of *l*-CSL on amphetamine-induced spontaneous locomotor activity in mice Amphetamine (Amp) augmented the spontaneous

locomotor activity of mice by inducing the release of DA from DA nerve endings. After Amp $10 \text{ mg} \cdot \text{kg}^{-1}$, the spontaneous locomotor activity (680 ± 99 times in 5 min) in mice was twice as that of NS group (329 ± 137), during the observing period of 5–10 min, as a hyperactive response. At the doses of 10, 20, 40, and $80 \text{ mg} \cdot \text{kg}^{-1}$ of *l*-CSL, both the normal activity (NS) and the Amp-hyperactive response were rapidly inhibited with a dose-response dependent manner. The peak activity was at 15–20 min after ip *l*-CSL but lasted for only about 20–30 min, except at high dose ($80 \text{ mg} \cdot \text{kg}^{-1}$) which lasted for about 3 h (Tab 5). In contrast to *l*-CSL, the low dose of Clo $1.25 \text{ mg} \cdot \text{kg}^{-1}$ remarkably inhibited the Amp-hyperactive response and the peak effect was on 3 h, then slowly recovered for a long period, even more than 8 h. Apparently, the effect of Clo prolonged quite more than that of *l*-CSL.

DISCUSSION

In the present work, the affinities to dopamine D_1 receptors of *l*-CSL, *dl*-CSL and *l*-SPD were active at the same level (K_i , 5.7–8.9 $\text{nmol} \cdot \text{L}^{-1}$), but to D_2 receptors, *l*-CSL and *dl*-CSL were more potent (K_i , 5.7–9.6 $\text{nmol} \cdot \text{L}^{-1}$) than *l*-SPD (K_i , 80 $\text{nmol} \cdot \text{L}^{-1}$). Obviously, the Cl on C_{12} of D ring of *l*-CSL increase the negative electronic charges on the D ring. Thus, it may enhance the affinity of *l*-CSL to

dopamine D_1 and D_2 receptors against *l*-SPD, particularly to D_2 . As to optical enantiomers of CSL to D_1 receptors affinity, *d*-CSL enantiomer (K_i , 135 $\text{nmol} \cdot \text{L}^{-1}$) was weaker than *l*-CSL. Furthermore, the affinity of *d*-CSL enantiomer to D_2 receptors was quite weaker (K_i , 9150 $\text{nmol} \cdot \text{L}^{-1}$) than *l*-CSL. Therefore, *l*-CSL enantiomer is really more potent one in the CSL enantiomers, while *d*-CSL is a less active enantiomer or inactive one to D_2 receptors. This action of CSL enantiomers is very similar to that of THP enantiomers^[16]. In other works, the *l*-enantiomer of THPB is active, and *d*-enantiomer is less active or inactive. The reason of different effects of THPB enantiomers to DA receptors has been explained by stereo and quantum chemistry in 1996^[17–18].

In the behavioral tests for DA receptor functions such as anti-seterotypy and catalepsy-induced in rats, anti-jumping and anti-locomotor activity in mice, all the enantiomers of CSL exhibited the antagonistic action on DA receptors, in which the *l*-enantiomer was the most potent one. Nevertheless, it has been demonstrated that *l*-CSL possesses the agonistic action to D_1 receptors by rotational behavior in 6-OHDA-lesioned rats, GTP regulation of R_H binding sites of *l*-CSL to D_1 receptors, and augmentation of adenylate cyclase activity in rat striatum (Chen LJ, *et al.*, unpublished data). All these results indicate that *l*-CSL possesses the intrinsic activity to D_1 receptors, and is D_1 agonist in the supersensitivity of D_1 receptors.

Tab 5. Effects of *l*-CSL on the spontaneous locomotor activity of mice. $\bar{x} \pm s$. $n=3$ times (9 mice). * $P < 0.01$ vs NS. ^f $P < 0.01$ vs Amp+NS.

Compound	Dose/ $\text{mg} \cdot \text{kg}^{-1}$	Locomotor activities (after ip) activity No./5 min						
		5–10	15–20	30–35	60–65	90–95	120–125	180–185
NS	–	329 ± 137	367 ± 137	385 ± 118	462 ± 157	500 ± 79	485 ± 53	469 ± 81
<i>l</i> -CSL	10	23 ± 36^c	231 ± 34^c	291 ± 61^c	539 ± 99	430 ± 63^c	461 ± 22	474 ± 61
<i>l</i> -CSL	20	9 ± 15^c	18 ± 18^c	300 ± 134^c	411 ± 135	501 ± 121	430 ± 126^c	437 ± 95
<i>l</i> -CSL	40	14 ± 26^c	7.8 ± 6.4^c	76 ± 73^c	337 ± 172^c	442 ± 101	378 ± 98^c	412 ± 53
<i>l</i> -CSL	80	2 ± 2^c	2 ± 2^c	8 ± 5^c	134 ± 120^c	188 ± 90^c	398 ± 14^c	423 ± 92
Amp+NS	–	680 ± 99	745 ± 44	702 ± 51	672 ± 51	598 ± 74	687 ± 100	548 ± 92
Amp+ <i>l</i> -CSL	10	70 ± 26^f	257 ± 67^f	743 ± 66	757 ± 86	703 ± 109	603 ± 47	379 ± 25
Amp+ <i>l</i> -CSL	20	91 ± 149^f	46 ± 25^f	607 ± 219	834 ± 86	671 ± 147	648 ± 157	684 ± 52
Amp+ <i>l</i> -CSL	40	15 ± 27^f	5 ± 9^f	153 ± 24^f	766 ± 61	544 ± 176	666 ± 116	492 ± 78
Amp+ <i>l</i> -CSL	90	1 ± 2^f	5 ± 8^f	239 ± 151^f	470 ± 165^f	608 ± 136	449 ± 308^f	374 ± 125^f
Amp+Cloz	1.25	216 ± 55^f	209 ± 37^f	182 ± 6^f	142 ± 84^f	151 ± 58^f	63 ± 32^f	57 ± 42^f

^fAmp $10 \text{ mg} \cdot \text{kg}^{-1}$

Recently, it has been found that *l*-SPD, *dl*-CSL and *l*-CSL had the protection of striatal injury by ischemia and MPP⁺-lesion (Jin GZ, *et al*, unpublished data, 1999).

Taken together, CSL enantiomers have the antagonistic (D₂)-agonistic (D₁) dual action, which is very similar to that of SPD.

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氯代斯阔任旋光异构体作用于多巴胺受体对动物行为的比较¹

R 971.2

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关键词 12-氯代斯阔任; 左旋千金藤立定; 阿朴吗啡; 多巴胺 D₁ 受体; Sch 23390; 放射配体测定; 刻板; 强直性木僵; 穿梭活动

药理

目的: 比较氯代斯阔任(CSL)旋光异构体对 DA 受体的作用特性. 方法: 采用小牛纹状体 DA 受体结合分析和小鼠、大鼠的行为实验. 结果: *d*-CSL 对 D₁ 和 D₂ 受体的 K_i 值分别是 135 和 9150 nmol·L⁻¹, 而 *l*-CSL 对 D₁ 和 D₂ 的亲合力(K_i)均为 5.7 nmol·L⁻¹, 分别为 *d*-CSL 的 24 倍和 1605 倍. *dl*-CSL 对 D₁ 和 D₂ 受体的 K_i 值分别为 8.9 和 9.6 nmol·L⁻¹, 比 *l*-CSL 稍弱. 大鼠刻板活动和木僵实验、小鼠的跳跃和自发活动实验均证明 CSL 旋光异构体对 DA 受体有阻滞作用. 结论: CSL 旋光异构体为 DA 受体阻滞剂的作用特性, 其作用强度为: *l*-CSL > *dl*-CSL > > *d*-CSL.

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