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Behavioral characteristics of olanzapine：an atypical neuroleptic

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KEY WORDS olanzapine；antipsychotic agents；dopamine；avoidance learning；catalepsy；electrophysiology；substantia nigra；ventral tegmental area

ABSTRACT

AIM：To assess the atypical neuroleptic properties of a novel antipsychotic agent，olanzapine (Ola). **METHODS**：The action of Ola on apomorpine (Apo)-induced climbing behavior，5-hydroxy-*dl*-tryptophan (5-HTP)-induced head twitch response，oxotremorine-induced tremor，and the conditioned avoidance behavior in mice were observed. The catalepsy of mice induced by Ola was also investigated. The single unit extracellular recording technique was used to compare the spontaneous firing rate changes of dopamine (DA) cells in the ventral tegmental area (VTA，A_{10}) and the substantia nigra pars compact (SNC，A_9) in rats after iv Ola. **RESULTS**：Ola antagonized the climbing behavior (ED_{50} 1.8 mg·kg^{-1}，*po*)，head twitch behavior (ED_{50} 0.3 mg·kg^{-1}，*po*)，and tremor (ED_{50} 5.2 mg·kg^{-1}，*po*) in mice. In a conditioned avoidance paradigm in mice，Ola inhibited the avoidance response with an ED_{50} of 2.72 mg·kg^{-1} (*po*). However，the catalepsy was not induced by Ola in mice even under a very high dose of 100 mg·kg^{-1} (*po*). Ola selectively increased the firing rate of DA cells in the VTA，but failed to affect that of SNC DA cells. **CONCLUSION**：Ola distinguished itself from the typical neuroleptic (eg haloperidol，Hal) and took resemblance of the atypical neuroleptic (eg clozapine，Clo) in 3 aspects：1) the multiple receptor pharmacodynamics involving D_1/D_2，5-HT_2 and M-ACh receptors；2) dose-response separation between the block of conditioned avoidance response and catalepsy induction；and 3) the specificity of action sites of firing rates upon acute drug challenge.

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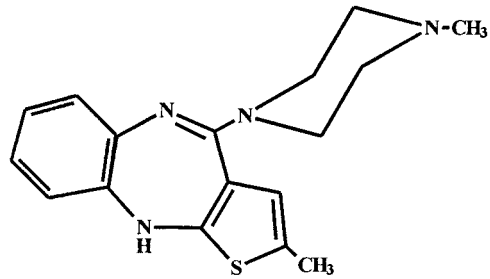
INTRODUCTION

An intense effort has been directed towards understanding how the mode of action of atypical antipsychotic drugs (eg clozapine，Clo) differs from that of the classical neuroleptic compounds (eg haloperidol，Hal).

Three notions have been utilized conceptually to explain the distinction between atypical versus typical antipsychotic drugs：1) separation of dose-response relationships between neurobehavioral or neuropharmacological parameters，that are analogous to antipsychotic drug-induced acute extrapyramidal side-effects (EPS) and antipsychotic effects in patients；2) specificity of action sites within the brain that may account for the difference in acute EPS liability between atypical and typical antipsychotic drugs as well as，perhaps，their differences in clinical efficacy；3) profile of neurotransmitter receptor interactions that characterize atypical antipsychotic drugs but are distinct from typical antipsychotics that may be casually related to the differences in side effect liability and/or efficacy in these two antipsychotic drug groups[1].



The chemical structure of olanzapine

Olanzapine {LY170053，2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno [2，3-*b*] [1，5] benzodiazepine，Ola} is supposed to be an "atypical" neuroleptic[2－3]. However，some of its pharmacological profiles and/or pharmaco-dynamics still need to be evaluated，particular-

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ly in its EPS and selectivity on the ventral tegmental area (VTA) neuron activity.

Based on the above mentioned conceptual bases for the mechanism of action of atypical antipsychotic drugs, behavioral and electrophysiological studies were undertaken to assess the atypical neuroleptic properties of Ola and its comparison with Clo and Hal.

MATERIALS AND METHODS

Animals Kunming Mice (♂, 19 g ± *s* 2 g) and Sprague-Dawley rats (♂, 250 g ± *s* 50 g) were provided by Shanghai Experimental Animal Center (Certification № 005 conferred by Animal Management Committee, Chinese Academy of Sciences).

Apo-induced climbing behavior in mice[4] Each mouse was put individually into a wire mesh cage (16 cm × 13 cm × 24 cm, mesh size 3 mm). Ola (provided by Shanghai Institute of Pharmaceutical Industry), Clo (Aldrich Chemical Company, Inc), Hal (Suzhou Pharmaceutical Factory) or vehicle were given (*po*) 60 min before apomorpine (Apo, Shenyang First Pharmaceutical Plant, 2.5 mg·kg^{-1}, sc) administration. Ten min later, the climbing behavior of mice was assessed at 5-min intervals for 20 min using the following scoring system: 0, no paw on the cage; 1, one paw on the cage; 2, two paws on the cage; 3, three paws on the cage; and 4, four paws on the cage. Climbing score at each time interval was then summed and expressed as a climbing index.

5-HTP-induced head twitch behavior in mice[4] Ola, Clo, Hal, or vehicle were administered (*po*) with nialamide (50 mg·kg^{-1}, ip) 60 min before the 5-hydroxy-*dl*-tryptophan (5-HTP, Sigma, 50 mg·kg^{-1}, ip). Twenty min later, the presence of head twitches was assessed at 10-min intervals for 30 min using the following scores: 0, absent; 1, moderate; and 2, marked.

Oxotremorine-induced tremor behavior in mice[4] Ola, Clo, Hal or vehicle were given (*po*) 2 h before oxotremorine (Sigma, 0.2 mg·kg^{-1}, iv). The tremor was scored 5 min later using the following scoring system: 0, absent, 1, slight, 2, moderate, and 3, marked.

Conditioned avoidance response in mice[4] Mice were trained to move from one side of a shuttle box (active conditioned avoidance box) to another upon a 5-s light presentation (conditioned stimulus). Failure to respond to the light was followed by light continuing and a mild electric current (0.5 mA) being applied to the grid floor (unconditioned stimulus) for a maximum of 10 s. Each animal received 10 trials per session with a 20-s intertrial interval. Crossings made during the conditioning stimulus period were recorded as avoidance responses, and those made during the unconditioned stimulus period were recorded as escape responses. Only those animals that showed a high level of avoidance response (> 80 %) were used in the study. Mice were administered (*po*) with Ola, Clo, Hal or vehicle 60 min before being placed in the shuttle box for the standard 10-trial session. The results were expressed as the percentage block compared with the vehicle-treated controls.

Induction of catalepsy in mice[5] Ola, Clo, Hal or vehicle were administered 30 min prior to testing. Catalepsy was determined by placing the animal on a wire grid. The time the animal maintained this position was recorded with a "cutoff" of 120 s, once an hour for 5 h. The time the animal remained on the rod at each recording was summed to give a maximum possible catalepsy time of 600 s.

Single unit extracellular firing recording in rats[6] After steady recording of the basal firing rate for 5 min, the drugs or vehicle were given to make comparison of the change of firing rate before and after the administration. For each animal, only one DA cell was selected for recording and histological verifications were made later to identify the precise recording location.

Statistics Results were expressed as $\bar{x} \pm s$ and analyzed by two-tailed *t*-test. The ED_{50} values were calculated by weighted probit analysis (Bliss and Finney).

RESULTS

Apo-induced climbing Ola [0.625 – 5 mg·kg^{-1}, *po*, ED_{50} 1.8 (1.5 – 2.3) mg·kg^{-1}], Clo [2.5 – 40 mg·kg^{-1}, *po*, ED_{50} 8.8 (6.8 – 11.3) mg·kg^{-1}] and Hal [(0.25 – 1) mg·kg^{-1}, *po*, ED_{50} 0.6 (0.3 – 1.1) mg·kg^{-1}] produced a dose-related block of Apo-induced climbing behavior (Tab 1). The results showed that Ola was about 3 times less active than Hal while 5 times more active than Clo in blocking apomorpine-induced climbing behavior.

5-HTP-induced head twitch Ola [0.16 – 1.25 mg·kg^{-1}, *po*, ED_{50} 0.3 (0.23 – 0.41) mg·kg^{-1}] also antagonized the twitch response, whereas Hal [(0.25 – 1 mg·kg^{-1}, *po*, ED_{50} 0.4 (0.12 – 1.6) mg·kg^{-1}] only reduced a slight effect at the highest dose (1 mg·kg^{-1}).

Tab 1. Effect of Ola, Clo, or Hal on climbing behavior induced by Apo (2.5 mg·kg^{-1}, sc). $\bar{x} \pm s$. $^bP < 0.05$, $^cP < 0.01$ *vs* vehicle-treated group.

Dose (mg·kg^{-1}, *po*)		Climbing index
Ola	0	13.9 ± 3.6
	0.625	14.0 ± 1.0
	1.25	9.7 ± 1.0
	2.5	3.9 ± 1.1^c
	5	0.8 ± 0.4^c
Clo	0	13.9 ± 3.6
	2.5	11.5 ± 1.3
	5	9.0 ± 1.0
	10	6.7 ± 1.3^b
	20	4.6 ± 1.3^c
	40	0.8 ± 0.5^c
Hal	0	13.9 ± 3.6
	0.25	13.2 ± 1.6
	0.5	7.4 ± 1.5
	1.0	3.2 ± 0.6^c

Ola was about 3 times as active as Clo [(0.625 – 5) mg·kg^{-1}, *po*, ED_{50} 1.1 (0.63 – 1.76) mg·kg^{-1}] in this model (Tab 2).

Tab 2. Effect of Ola, Clo, or Hal on head twitches induced by 5-HTP (50 mg·kg^{-1}, ip) in nialamide (50 mg·kg^{-1}, ip) pretreated mice. $\bar{x} \pm s$. $^bP < 0.05$, $^cP < 0.01$ *vs* respective vehicle-treated group.

Dose (mg·kg^{-1}, *po*)		Score
Ola	0	4.4 ± 0.3
	0.16	3.0 ± 0.3
	0.32	2.8 ± 0.2^b
	0.625	0.6 ± 0.3^c
	1.25	0.3 ± 0.8^c
Clo	0	4.4 ± 0.3
	0.625	3.1 ± 0.5
	1.25	1.7 ± 0.5^b
	2.5	1.0 ± 0.4^c
	5	1.0 ± 0.3^c
Hal	0	4.4 ± 0.3
	0.25	2.7 ± 0.7
	0.5	2.5 ± 0.4
	1.0	1.0 ± 0.2^c

Oxotremorine-induced tremor Ola produced a marked block of oxotremorine-induced tremor at all doses tested [(2.5 – 10) mg·kg^{-1}, *po*, ED_{50} 5.2 (2.1 – 12.9) mg·kg^{-1}]. Likewise, Clo [(5 – 20) mg·kg^{-1}, *po*, ED_{50} 14.1 (3.9 – 50.3) mg·kg^{-1}], also antagonized the tremorogenic effect of oxotremorine. Hal, even at very high doses (5 and 10 mg·kg^{-1}, *po*), had no effect on the response (Tab 3).

Tab 3. Effect of Ola, Clo, or Hal on oxotremorine (0.2 mg·kg^{-1}, iv)-induced tremor in mice. $\bar{x} \pm s$. $^bP < 0.05$, $^cP < 0.01$ *vs* the vehicle-treated group.

Dose (mg·kg^{-1}, *po*)		Score
Ola	0	2.9 ± 0.1
	2.5	2.2 ± 0.2^b
	5	1.7 ± 0.3^c
	10	0.6 ± 0.2^c
Clo	0	2.9 ± 0.1
	5	2.5 ± 0.3
	10	1.7 ± 0.1^c
	20	1.2 ± 0.3^c
Hal	0	2.7 ± 0.1
	5	2.5 ± 0.2
	10	2.3 ± 0.2

Conditioned avoidance and catalepsy Ola produced a dose-related block of avoidance response (CAR). A dose of 2.5 mg·kg^{-1} *po* produced about 50 % block of CAR, whereas 10 mg·kg^{-1} *po* virtually abolished the CAR. Similar to Clo (50 – 150 mg·kg^{-1}, *po*), Ola failed to produce catalepsy (CAT) (Fig 1, Tab 4). The ratio of ED_{50} CAT (more than 100 mg·kg^{-1})/ED_{50} CAR [2.72 (2.02 – 3.66) mg·kg^{-1}] is more than 100. This more than 100-fold selectivity for blocking CAR was in clear contrast to that in Hal (0.125 – 0.5 mg·kg^{-1}, *po*), which possessed (ED_{50} CAT/ED_{50} CAR) ratio of less than 3.

Tab 4. Effect of Ola, Clo, and Hal on conditioned avoidance response (CAR) and the induction of catalepsy (CAT) in mice. Results were expressed as ED_{50} values (mg·kg^{-1}, *po*) with 95 % confidence limits stated in parentheses. The ratio is the ED_{50} CAT/ED_{50} CAR. NA = not applicable.

Compounds	ED_{50} CAR (mg·kg^{-1}, *po*)	ED_{50} CAT (mg·kg^{-1}, *po*)	Ratio
Ola	2.72 (2.02 – 3.66)	> 100 NA	> 100
Clo	21.3 (15.4 – 29.4)	> 100 NA	> 100
Hal	0.27 (0.14 – 0.54)	0.70 (0.31 – 1.56)	2.6

Different effects of Ola on the spontaneous activity of VTA and SNC DA neurons in rats Ola (0.1 – 0.8 mg·kg^{-1}, iv) increased the firing rate of 5/7 tested VTA DA cells (56 % ± 9 % – 268 % ± 43 %

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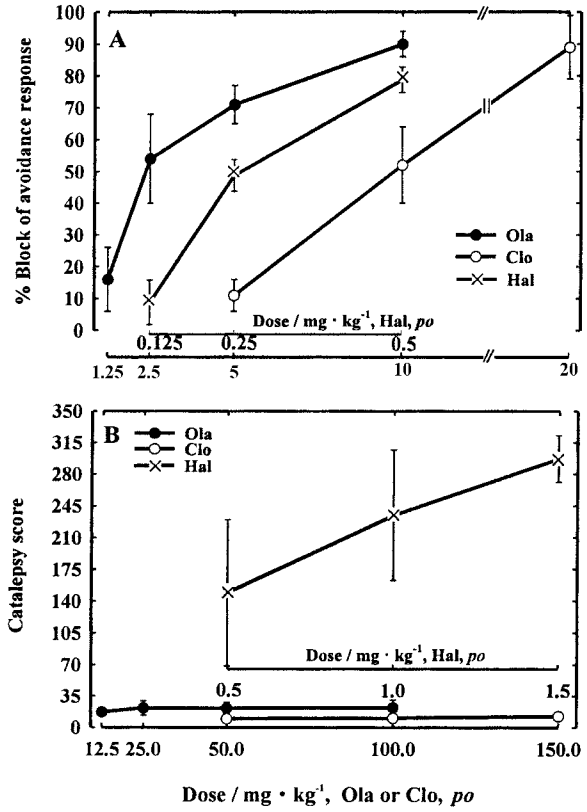

Fig 1. (A) Effect of Ola on conditioned avoidance responding in the mice. $n = 6 - 8$ mice. The results were expressed as $\bar{x} \pm s$ percentage block of avoidance response. (B) Ola induced catalepsy in rats. The results were expressed as $\bar{x} \pm s$ total CAT time assessed at 1-h intervals for 5 h. A score of 600 is the maximum possible for each rat.

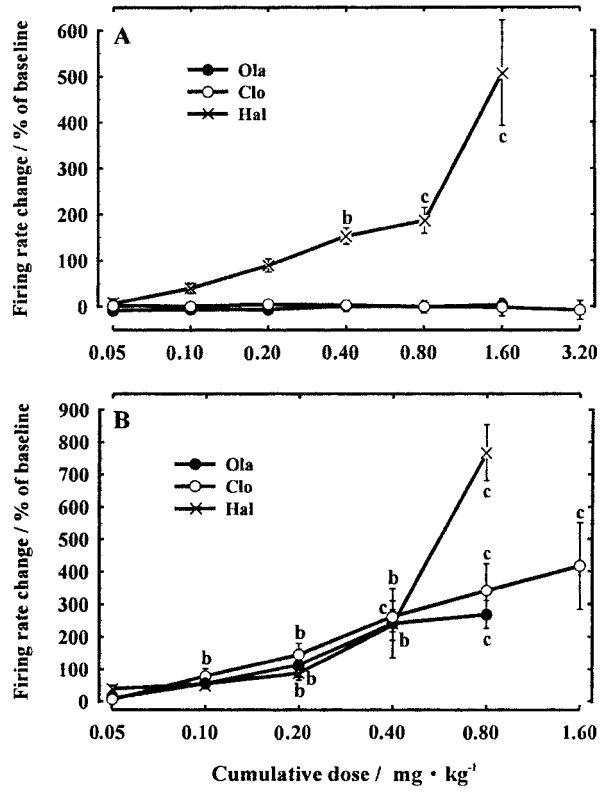

Fig 2. Effects of acute Ola, Clo, or Hal (0.05 mg·kg^{-1} – 3.2 mg·kg^{-1}, iv) on the spontaneous firing rate of DA neurons in substantia nigra pars compact (SNC) (A) and the ventral tegmental area (VTA) (B) in rat brain. $n = 5 - 6$ rats, $\bar{x} \pm s$. $^{b}P < 0.05$, $^{c}P < 0.01$ *vs* the baseline.

above the baseline). In the SNC, however, Ola failed to cause the firing rate of most tested DA cells (−8.7 % ±2.4 % −3.9 % ±8.7 % of the baseline) even at the maximum cumulative dose of 1.6 mg·kg^{-1}.

Clo acted in much the same way as Ola in both VTA (146 % ±34 % − 416 % ±83 % above the baseline) and SNC (−7.7 % ±20.3 % −5.3 % ±8.8 % of the baseline). Thus, Ola showed its preferential action in VTA than in SNC similar to the atypical neuroleptic Clo upon acute administration.

Hal (0.2 − 0.8 mg·kg^{-1}, 0.4 − 1.6 mg·kg^{-1}, iv, respectively) increased both the VTA (88 % ±13 % − 767 % ±87 % of the baseline) and the SNC (153 % ± 18 % −508 % ±115 % of baseline) firing rate in DA cells in the same manner, which showed lack of selective action on the VTA and the SNC DA system (Fig 2).

DISCUSSION

The present studies demonstrates that Ola, resembles the prototype atypical antipsychotic Clo, has a broad pharmacological profile, in which, the DA M-ACh, 5-HT-nergic systems are involved.

Ola was equipotent in antagonizing Apo-induced climbing behavior and blocking of conditioned avoidance response, demonstrating that it possessed DA receptor antagonist activity, because both experiments are widely used for the assessment of antipsychotic activity[7-9], and, therefore, predict that Ola possesses antipsychotic activity.

Besides, Ola also possessed anticholinergic activity, as measured by the antagonism of oxotremorine-induced tremor, at doses similar to those required for its DA antagonist activity. Therefore, a number of evidences suggested that an anti-muscarinic component of Ola might eliminate the cataleptic profile (or EPS) of some atypical antipsychotic drugs[10]. It has also been shown that 5-HT antagonist activity may also abolish the cataleptogenic activity of compounds[11]. Like Clo, Ola is a more potent inhibitor of 5-HTP-induced head twitch, a test asso-

ciated with 5-HT_2 antagonist activity[12], than Apo-induced climbing behavior. Thus, *in vivo*, Ola is about 6 times more potent as a 5-HT_2 antagonist than as a dopamine antagonist. As discriminate function analysis of atypical antipsychotic drugs show, a relatively less D_2 activity to 5-HT_2 affinity either *in vitro*[13] or *in vivo*[14] binding assay studies is the characteristic of an atypical profile.

The weak, or negligible catalepsy induced in animals, which is associated with an antipsychotic drug eliciting acute EPS in the clinic, is one of the most important discriminatory tests between atypical and typical antipsychotic drugs[5,15]. Atypical antipsychotics distinguish themselves by their relatively greater separation of dose-response curves for antipsychotic efficacy and EPS liability than the typical neuroleptics. In animal models, atypical antipsychotics would be expected to have cataleptogenic doses that far exceed the doses required to antagonize the retention of a conditioned avoidance response which serves as model for antipsychotic activity[4,16]. In the present studies, Ola had a ratio (ED_{50} CAR/ED_{50} CAT) of more than 100, compared with 2.6 for Hal (Tab 4). The marked separation between doses of Ola that block conditioned avoidance response and doses-inducing catalepsy suggest that Ola will be less likely to induce unwanted EPS at therapeutically useful doses. It is interesting to note that ED_{50} CAR/ED_{50} CAT induced in Ola was similar to that of Clo, another atypical compound. The high dose of Ola required to produce catalepsy may be due to a combination of the 5-HT_2 antagonist and anticholinergic activity of the compound.

As is well-known, the specific mesocorticolimbic effect on VTA DA cell activity rather than the SNC DA cells, namely the more selective antipsychotic action, is believed to be one of the explanations for the different action of atypical versus typical neuroleptics. It has been found that acute Ola, like Clo, elevated the firing rate of VTA DA cells, but did not change the activity of the great majority of non-DA cells in the VTA or of adjacent SNC DA units. On the other hand, acute Hal accelerated the firing rate of both VTA and SNC DA neurons at similar doses. The lack of acute effect of Clo on SNC cells is consistent with the data reported by Stockton and Rasmussen[17] and the selective action of Ola and Clo on VTA DA neurons is in accord with a report showing that acute Clo activates VTA but not SNC DA neurons[18].

In conclusion, Ola has a profile of activity similar to that of the atypical agent Clo. It is a potent 5-HT_2/D_2 antagonist with anticholinergic activity, which possesses a selective action on VTA DA cells and has great ED_{50} CAR/ED_{50} CAT ratio. Therefore, it may indicate that Ola has an atypical profile and will be less likely to induce undesirable EPS in the clinic.

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非经典安定剂奥氮平的行为学特性

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关键词　奥氮平；抗精神病剂；多巴胺；回避学习；僵住症；电生理学；黑质；腹侧被盖区

目的：评价新型抗精神病药物奥氮平（Ola）的非经典安定剂特性. 方法：用细胞外单位放电记录技术分析中脑腹侧被盖区（VTA）和黑质致密区（SNC）多巴胺（DA）神经元自发放电活动. 结果：Ola 对抗小鼠攀爬行为、头部抽动行为、震颤行为及小鼠的条件回避行为，但在 100 mg·kg^{-1}的高剂量下仍不能诱发小鼠的僵住症. Ola 增加大鼠 VTA 但不影响 SNC DA 神经元的放电活动. 结论：1）Ola 具有 D_1/D_2，5-HT_2 和 M-ACh 多种受体的药效学相互作用的特性；2）对抗条件回避行为和诱发僵住症的不同效应有剂量区别；3）急性给药引起细胞放电频率变化的作用部位有特异性.

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