Comparison of the effects of antipsychotic drugs in two antipsychotic screening assays: swim-induced grooming and apomorphin climbing test in mice

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Introduction

The antagonism of apomorphine-induced climbing behaviour and sniffing and the swim-induced grooming test are widely used models for screening antipsychotic drugs. It is hypothesized that blockade of climbing behaviour evoked by apomorphine is related to the dopamine receptor blockade in the nucleus accumbens and antagonism of stereotyped sniffing produced by apomorphine is related to the blockade of dopamine D2 receptors in the striatum [1]. The dopamine receptor antagonist antipsychotics inhibit both apomorphine-induced behaviours, although compounds with strong 5-HT2A inhibitory effect show higher potency in blocking the climbing vs. the sniffing response. The grooming behaviour induced by immersion in water involves mainly dopamine D1 receptors [2]. This behaviour is inhibited in a dose dependent manner by dopamine receptor antagonists. [3]. The aim of our study was to compare these two screen assays in terms of their sensitivity to the actions of various antipsychotic compounds. We investigated the effect of a conventional neuroleptic (haloperidol), atypical antipsychotics (clozapine, olanzapine, risperidone, ziprasidone, amisulpride) and new generation, partial D2 agonist antipsychotics (arpiprazole, bifeprunox) in these screening methods.

Methods

Climbing and sniffing Male CD-1 mice were injected orally with the test compound or vehicle. Fifty minutes later the animals were placed into cylindrical cages, with walls of vertical metal bars 2 mm diameter 1 cm apart, surmounted by a smooth surface. After 10 minutes habituation the mice were treated with apomorphine (1.5 mg/kg sc.). Ten minutes after APO treatment each animal was observed for 15 minutes. Every minute the climbing behaviour was scored as follow: four paws on the floor (0), forefeet grasping the wall (1), four paws grasping the wall (2). Animals were also rated for repetitive sniffing as a measure of stereotypy according to the following scale: 0 = no sniffing, 1 = moderate sniffing, little snout contact with cage walls or floor, 2 = constant sniffing, persistent snout contact. Scores for both behaviours were summed for each individual and group means were calculated. Drug effect was expressed and plotted as percentage inhibition of the apomorphine-induced behaviour. Dose-response curve was plotted for each compound and ED_{50} values were determined by linear regression.

Swim incuced grooming in mice Male NMRI mice were used. Sixty minutes after drug treatment, mice were placed individually in swimming cylinders filled with waterfor 3 min. They were then removed and dried with towel for 30 sec. and placed immediately into single perspex boxes. The number and the total duration of grooming episodes in seconds were recorded for 15 min. Dose-response curve was plotted for each compound and ED_{50} values were determined by linear regression.

Results

ED_{50} values of antipsychotics in apomorphine-induced climbing and sniffing and swim-induced grooming test are summarized in Table 1. Apomorphine-induced climbing and sniffing were potently and dose-dependently blocked by the compounds. The order of potency of antipsychotics on climbing inhibition was bifeprunox = risperidone ~ haloperidol > aripiprazole ~ olanzapine > ziprasidone ~ clozapine >> amisulpride. The order of potency of antipsychotics in blocking sniffing was bifeprunox > haloperidol ~ risperidone > aripiprazole > olanzapine = ziprasidone >> amisulpride > clozapine.

Post-swimming grooming time was inhibited dose-dependently by risperidone = bifeprunox > haloperidol > olanzapine > clozapine > aripiprazole = ziprasidone. Interestingly, amisulpride elevated rather than decreased the grooming time at doses of 30 and 60 mg/kg ip while it had no effect after 120 mg/kg ip.

Table 1. *Oral ED_{50} values of antipsychotics in the apomorphine antagonism and swim-induced grooming test. Values are in mg/kg.*

	Apomorphine-induced		Swim-induced
	climbing	sniffing	grooming time
Haloperidol	0.17	0.32	0.65
Clozapine	5.3	18	2.1
Olanzapine	1.3	4.4	1.2
Risperidone	0.12	0.45	0.30
Aripiprazole	0.97	2.2	5.1
Bifeprunox	0.1	0.14	0.38
Ziprasidone	3.9	4.6	5.4
Amisulpride (ip.)	30	12	increase

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Conclusion

Compound which showed potent apomorphine-induced climbing inhibition relative to sniffing inhibition (risperidone, olamzapine, clozapine) have high 5-HT_{2A} receptor antagonist effect. Olanzapine and clozapine, which have considerable dopamine D1 receptor antagonist effect, showed potent blockade of swim-induced grooming relative to their climbing inhibition.

As the two widely used screening methods showed different sensitivity to the various antipsychotics their parallel use in antipsychotic screening systems is therefore warranted.

References

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