Back-translation from clinic to animal test: efficacy of current and past antipsychotics in the attenuation of d-amphetamine induced hyperlocomotion in Wistar-Han rats

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Introduction: D-amphetamine induces symptoms of psychosis like those of schizophrenia in healthy individuals and aggravates them in schizophrenic patients[1]. Locomotor activity (LMA) in rodents can be manipulated during investigation of pharmacological agents concerning mania[2]. The aim of the present study was to investigate the pharmacodynamics of clinically-used antipsychotics in a drug-induced animal test, evaluating the clinical back-translation of these antipsychotics. The D_2-selective antagonist sulpiride was utilized as a negative control due to its poor blood-brain-barrier permeability thus lack of effect at low doses[3].

Methods: Adult male Wistar-Han rats were randomly grouped into dose groups/ saline alone ± d-amphetamine per antipsychotic (n=8) respectively. Rats were habituated in LMA arenas for 60-min prior to antipsychotic pretreatment of haloperidol (0.03, 0.1, 0.3), risperidone (0.1, 0.3, 1), clozapine (1, 3, 10, 30), aripiprazole (1, 3, 10, 30) and sulpiride (1, 3, 10, 30, 100) [s.c./i.p. mg/kg]. After 30-min, d-amphetamine was injected (s.c.) and data was recorded for 210-min. The total ambulatory move time was measured using TruScan-2 (Coulbourn-Instruments). Plasma was taken 60-min post-antipsychotic administration in satellite rats of similar weight, sex and age for HPLC analysis. The data is given as mean±SEM and analysed via one-way ANOVA with Dunnett's test.

Results: A dose-finding study indicated 1.5 mg/kg d-amphetamine as the active dose against antipsychotics to be tested. A dose-response was demonstrated with all antipsychotics apart from sulpiride (doses < 30 mg/kg). The minimum effective dose (MED) showing significant attenuation of amphetamine-induced hyperlocomotion with plasma exposure was determined for free drug concentration calculation ($C_{u,brain}$) (Table 1).

	Minimum effective dose in rat (mg/kg)	Significance against d-amphetamine (P value)	C_{plasma} (Mean±SEM nM)	Mean estimated $C_{u,brain}$ in rat (nM)	Estimated $C_{u,brain}$ therapeutic range in human (nM)
Haloperidol	0.1	<0.001	4 ± 1.1	0.28	0.15 – 0.35
Aripiprazole	3	<0.01	32 ± 20.8	0.32	0.64 – 1.27
Risperidone	0.1	<0.001	38 ± 3.1	1.60	1.49 – 4.46
Clozapine	10	<0.0001	744 ± 56.8	18.97	90.7 – 108.8
Sulpiride	30	0.0093	15800 ± 1312	6952	6.24 – 98.5

Table 1. The MED of different antipsychotics in rats and their plasma concentration with estimated $C_{u,brain}$ in rat brain [1]. The therapeutic range was taken from publication and calculated as $C_{u,brain}$ [2].

[1]: $Rat\ Cu,brain = \frac{fu,plasma*}{Efflux\ Ratio\ (x>1)*} \times Cplasma$

[2]: $Cu,brain = (\text{human therapeutic plasma range}) \times (f_{u,plama}) * \times \left(Kp,uu,\frac{brain}{plasma}\right) *$

*risperidone and clozapine *in-vitro* data provided by Boehringer Ingelheim & others found in literature [4, 5, 6, 7]

***Conclusion*:** The results above indicate hyperlocomotion targeted pharmacodynamics and display the estimated $C_{u,brain}$ in rat at MED of all apart from sulpiride is within 5-fold range of estimated $C_{u,brain}$ of the known therapeutic plasma range in humans. Clozapine disconnection could be attributed to species differences in metabolism and active metabolites. As the pre-clinical correlates with clinical exposure, it suggests that this amphetamine-induced hyperlocomotion behavior test is suitable for pre-clinical MED for novel antipsychotics.

References:

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