

THE CONDITIONED AVOIDANCE RESPONSE TASK. EFFECTS OF CS MODALITY ON AVOIDANCE LEARNING AND ANTIPSYCHOTIC SENSITIVITY.

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INTRODUCTION

Conditioned Avoidance Response (CAR) is frequently used in current antipsychotic drug development and is commonly considered a reliable screening tool, with high predictive validity, for the detection of potential antipsychotic activity. Antipsychotics (APDs) have the unique ability to selectively suppress the CAR behavior.

In a typical CAR study, a rat is placed in a two-compartment shuttle box where a neutral conditioned stimulus (CS, auditory or visual) is presented and, after a short delay, is followed by an aversive unconditioned stimulus (US, weak foot-shock). The animal may **escape** the US by switching compartment. Training (performed by repeating presentations of CS-US pair) will lead to **avoidance** of the US i.e. the rat will switch compartment during the CS and before the onset of the US.

Well performing animals treated, with low (non cataleptic) doses of APDs fail to perform avoidance responses to the CS, even though their escape response to the shock itself is relatively unaffected. This selective disruption of avoidance is a characteristic of all APDs and the ability of an APD to suppress CAR has been shown to be closely correlated with its clinical potency. Therefore, suppression of avoidance in CAR is correlated with the specific antipsychotic action of APDs.

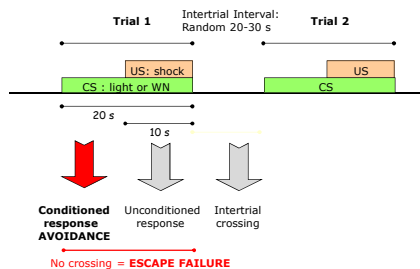
In the present study, we investigated the impact of a visual (light) or an auditory (white noise) CS on both the rate of learning and the response to various APDs: haloperidol, risperidone, clozapine and olanzapine. Dose-dependent suppression of the avoidance behavior and the effects of the APDs on escape behavior (i.e. escape failures) were recorded.

MATERIALS AND METHODS

ANIMALS Male Wistar rats, 200-250 g, 2 to 4 individuals per cage
Housing conditions: temperature: 22 ± 2 °C, hygrometry 55 ± 10%, 12/12h light/dark cycle, water and food *ad libitum*

DRUGS All drugs were administered via the s.c. route 30 min before the CAR session
Haloperidol, risperidone, clozapine and olanzapine were dissolved in saline -0.1% HCl

CAR TEST Shuttle-boxes with light or white-noise (WN) as CS, soundproof boxes
Training and testing: 1 session of 30 trials per day
Training: performance criterion of 80% of correct response for at least 2 consecutive days
Testing: cross-over study design

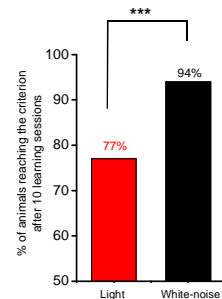


EXPERIMENTAL PARAMETERS
Avoidance = response to CS
Escape failure = failure to respond to CS + US

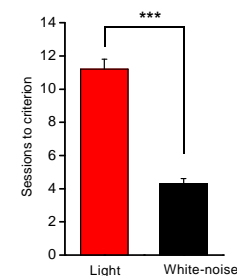
STATISTICAL ANALYSIS Two-way ANOVA (time, treatment) and Student's t test

RESULTS

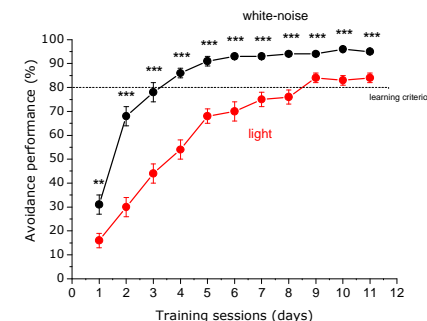
CAR TRAINING PHASE



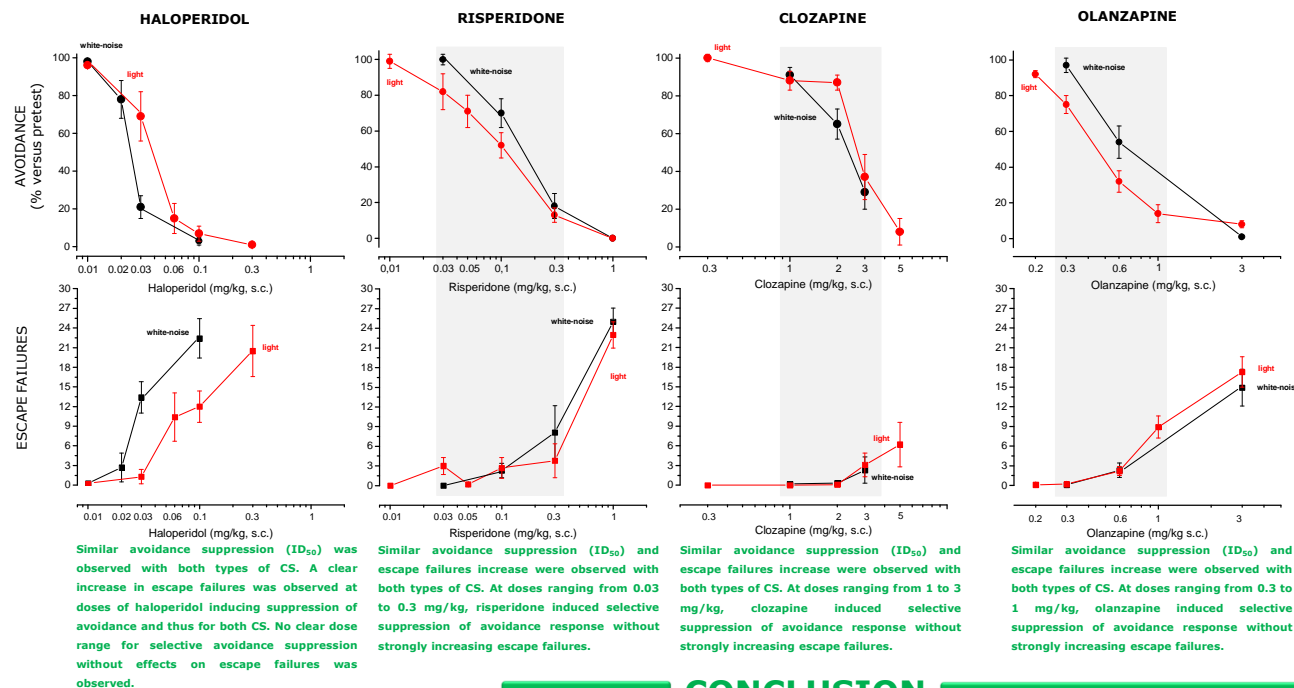
Inclusion rate is higher when using white-noise as CS.



Rats learn faster with white-noise as CS and displayed a higher stabilized performance when overtrained.



ANTIPSYCHOTIC TESTING



CONCLUSION

Using white-noise as CS, training is faster and inclusion rate is higher. Suppression of avoidance response by APDs was very similar whatever the CS modality used. A dose range of selective effects (with a suppression of avoidance response without a large increase in escape failures) was defined for all atypical antipsychotics, but not for haloperidol. In conclusion, the sensitivity to various antipsychotic agents in this paradigm is not dependent on the CS modality. However, using an auditory stimulus, Wistar rats clearly acquired the avoidance response faster, suggesting that the auditory stimulus is more salient than the visual one.

ID_{50}	Haloperidol	Risperidone	Clozapine	Olanzapine
Light	0.024 mg/kg	0.15 mg/kg	2.38 mg/kg	0.45 mg/kg
White-noise	0.038 mg/kg	0.11 mg/kg	2.68 mg/kg	0.68 mg/kg