Cognitive deficits such as impairments in cognitive flexibility, attention and working memory are a core feature of schizophrenia that are minimally responsive to current antipsychotic drugs. Impairments in cognitive flexibility, such as set-shifting and reversal learning are consistently found in schizophrenia and are attributed to disrupted prefrontal cortex function. In tests such as the Wisconsin Card Sorting test (WCST), patients show impairments in different rules or strategies, exemplified by impairments in the intra-/extra dimensional (ID/ED) task in a computerised version of the WCST.

We have previously demonstrated that subchronic intermittent phencyclidine (PCP) treatment in rats produces cognitive deficits as well as alterations in brain function and neurochemistry akin to those seen in schizophrenia (Pratt et al., 2008).

Cognitive deficits in animal models can be assessed using the Attentional Set-Shifting Test (ASST) (Figure 1), an adapted version of the WCST for use in rodents (Birrel & Brown, 2008).

Recently, clinical trials have shown that modafinil improves cognitive deficits in the ASST in schizophrenic patients (Turner et al., 2004).

Here we further validate the subchronic PCP model as a translational model of schizophrenia by investigating the ability of modafinil to reverse PCP-induced cognitive deficits in the ASST.

METHODS

• Male Lister Hooded rats received either subchronic vehicle (saline, i.p.) or PCP (2.58mg.kg-1, i.p.) 1 x daily for 5 days. 72 hours after the final treatment animals were tested in the ASST as previously described (Egerton et al., 2005).

• 30 minutes prior to behavioural testing animals received either acute Modafinil (64 mg.kg-1, p.o.) or vehicle (5% methylcellulose). Acute treatment was also repeated 30 minutes prior to the fourth discrimination in the ASST due to the short half-life of modafinil.

• During the test session rats performed a series of discriminations in the order outlined in Table 1. The identity of the exemplar combinations employed in the ASST, and their pairings, are outlined in Table 2.

• Data was analysed by ANOVA, Mann-Whitney U- or t-test. Bonferroni correction was applied for multiple comparisons as appropriate.

RESULTS

• The subchronic intermittent PCP treatment regime used in this study induces deficits in cognitive flexibility that model both the set-shifting impairment seen in schizophrenia and also the reversal learning deficits reported in this disorder.

• PCP-induced deficit in reversal 3 appeared to be due to regressive errors rather than perseverative responding.

• Acute treatment with modafinil improves PCP-induced set-shifting deficits, similar to results observed in set-shifting tests in schizophrenic patients, but does not improve reversal learning deficits.

• These results show that modafinil modulates distinct cognitive domains in the ASST and further validates the subchronic PCP model as a translational model to identify compounds that target the unique therapeutic need in schizophrenia.

CONCLUSIONS

REFERENCES


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