Methamphetamine cross-sensitizes to stimulatory effects of modafinil on locomotor mouse behaviour

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Introduction

Modafinil (MOD) is a drug used for its psychostimulant effect in a treatment of ADHD, narcolepsy and fatigue caused by sleep disorder syndromes. It is studied today in relation to its suitability for a drug dependence treatment, including methamphetamine (MET) abuse. Experimental studies and clinical trials describe either mild positive effect and some not very optimistic results, e.g. more drug-free urine samples in a group of patients treated with MOD [1] or no effect in comparison with placebo [2,3]. This uncertainty might be based on a fact, that the mechanism of action of MOD is not fully understood. Previously, our research group approved that repeated administration of MOD induces behavioural sensitization to its stimulatory effect on locomotor activity in mice [4]. Phenomenon of behavioural sensitization is known to result from neuroplastic changes in a drug dependent brain. This may interact with pharmacotherapeutical treatment efforts. Thus evidence of functional interactions between behavioural effects of MOD and psychostimulants is important in considering appropriate dependence therapy.

Aim

To assess an impact of methamphetamine and modafinil interactions on psychostimulant effects in mice.

Methods and time schedule

On the experimental Day 1, adult male mice of SPF ICR outbred strain were randomly allocated into four groups (n=15; n=15; n=14; n=15). From the Day 7 to 13, an i.p. pretreatment was provided daily as follows in the Table below. On the Day 14, “challenge” dose of MOD was administered as is shown in the Table below. Locomotor activity in the Open Field Test was recorded for 3 min by Actitrack (Panlab, Spain). The measurement of trajectories was performed on the Days 1, 7 and 14. Data were analyzed using two-way ANOVA test with Bonferroni post-tests.

Results

Mice were separated into four fully comparable groups which was verified in the first open-field trajectory measurement. There were no significant differences in locomotor activity exhibited by all groups of drug-naive mice. In the second measurement, acute dose of drugs chosen for the pretreatment (MET, MDMA) showed increase (p<0.001) in the mouse locomotor activity. The acute dose of MOD significantly (p<0.001) increased locomotor activity only in MET pretreated mice in comparison with vehicle effects. No analogous changes were observed in MDMA pretreated mice, only a potential trend which did not reach statistical significance.

Conclusion and discussion

This experiment shows that acute dose of MOD, which did not change the locomotor activity of mice administered alone, caused a significant psychostimulation given after repeated pretreatment with MET. This should be taken into account when considering a risk/benefit ratio of the psychostimulant dependence therapy with MOD. However, a long term behavioural sensitization is known to develop after repeated administration of MET [5]. Thus the present results suggesting increase in psychostimulant effects of MOD after pretreatment with MET might also be associated with persistence of MET behavioural sensitization. This has to be evaluated by further studies.

References


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