BEHAVIORAL PROFILING OF STIMULANTS AFTER ACUTE ADMINISTRATION IN RATS USING LABORAS™

Toni Wolinsky, Leann Quinn, David Virley, Vincent Castagné, Paul Moser

INTRODUCTION

Preclinical evaluation of abuse potential is often performed too late during the drug development process to guide decision-making. Automated behavioral measurements of motor activity cannot differentiate stimulants with or without abuse liability while the measurement of non-motor behavior generally requires non-automated and subjective observational methods. Interpretation of data from different methods is complicated by interactions of the animals with their testing environment.

The LABORAS™ (Laboratory Behavior Observation, Registration and Analysis System, Metris b.v., The Netherlands) is an automated system able to analyze motor and basic non-motor behaviors in rodents. The purpose of the present study was two-fold: 1) to describe the behavioral profile of know stimulant substances , and 2) to evaluate the ability of LABORAS™ to differentiate between the substances, particularly as a function of their abuse potential.

MATERIAL & METHODS

Studies were performed at Porsolt SAS facilities using naïve male Rj:Wistar (Han) rats (180 - 230 g). All substances were purchased commercially. The doses tested were: cocaine 1.25, 2.5, 5, 10, and 20, amphetamine 0.3, 1 and 3, MK-801 0.03, 0.1, 0.3 and 1, ketamine 3, 10, 30 and 60, modafinil 15, 30, 60 and 120 and nicotine 0.1, 0.3 and 0.9 (mg/kg of supplied substance, except for nicotine, base substance). Test substances were dissolved in physiological saline, except for modafinil which was suspended in 0.2% hydroxypropylmethyl cellulose in physiological saline. The test substances and their vehicle were injected subcutaneously (s.c.). Experiments were performed blinded.

Immediately after dosing, the animals were individually placed into covered polycarbonate cages (37 x 21 x 24 cm) in the LABORAS™ system, all of which resided in an illuminated testing room. Data were automatically analyzed for horizontal and vertical activity as well as for grooming, drinking, feeding and immobility. Data were analyzed over 10-minute intervals using 2-way ANOVA (time X treatments), followed by 1-way ANOVA (treatment) and Dunnett's two-tailed test (comparing test substance dosing groups with vehicle control at each testing time) for post hoc analysis. The level of significance was set at $P < 0.05$.

RESULTS

Fig. 1

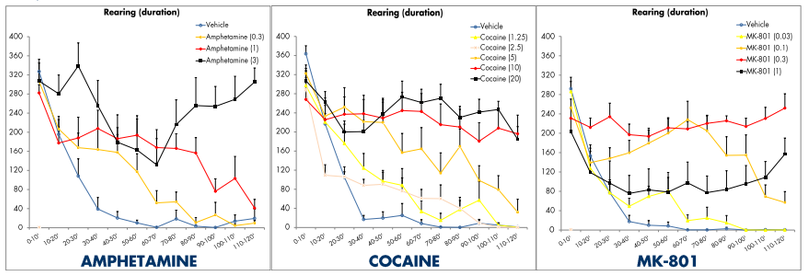

Figure 1: Duration of rearing. Cocaine displayed similar increasing effects on rearing and locomotion. Amphetamine increased rearing in a dose-dependent manner at 1 and 3 mg/kg, these effects being biphasic at the higher dose. MK-801 initially decreased rearing at the higher dose but then displayed stimulant-like activity at 0.1, 0.3 and 1 mg/kg. Interestingly effects demonstrated at the higher dose of MK-801 were delayed when compared with lower doses.

Effects of the test substances on motor behavior

Fig. 2

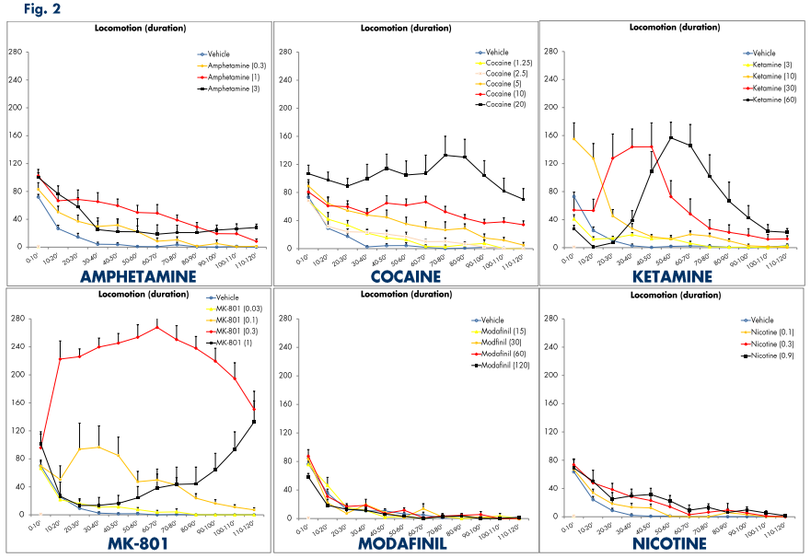

Figure 2: Duration of locomotion. Cocaine dose-dependently increased locomotion at 5, 10 and 20 mg/kg, maximal effects were observed around 70-90 minutes at the highest dose. Amphetamine and MK-801 had maximal effects at intermediate doses of 1 and 0.3 mg/kg, respectively. MK-801 displayed peak activity around 70 minutes. Ketamine dose-dependently increased locomotion at 10, 30 and 60 mg/kg, maximal effects being observed between 50 and 70 minutes at high dose. Modafinil was devoid of effects up to 120 mg/kg whereas nicotine weakly increased locomotion at 0.3 and 0.9 mg/kg between 20 and 60 minutes.

Fig. 3

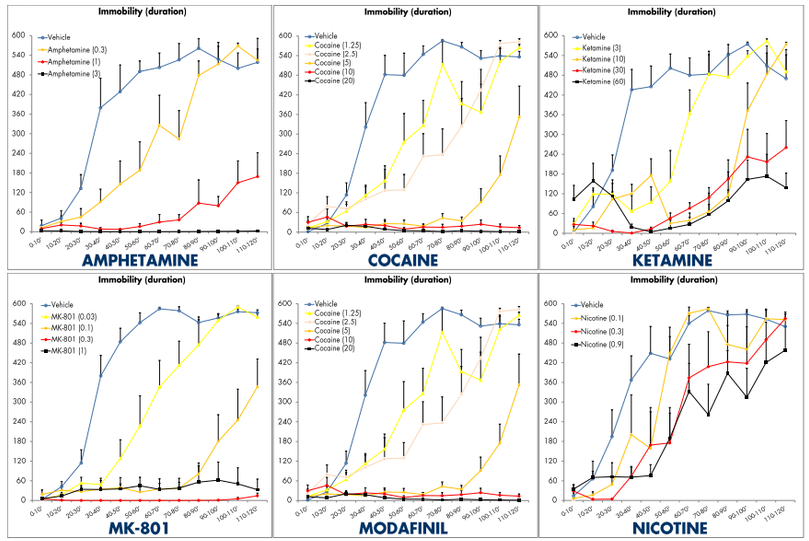

Figure 3: Duration of immobility. Apart from modafinil which was inactive and nicotine which was weakly active, the other test substances markedly and dose-dependently decreased immobility at doses lower than the doses increasing locomotion.

Effects of the test substances on non-motor behaviors

Fig. 4

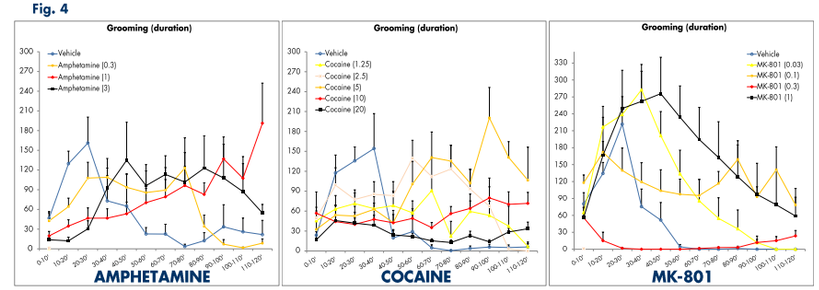

Figure 4: Duration of grooming. Cocaine initially decreased grooming at 5, 10 and 20 mg/kg, in contrast, it stimulated grooming at low doses between 60 and 120 minutes. Amphetamine also initially decreased grooming at 0.3, 1 and 3 mg/kg with opposite effects at high doses during the last period of the test. MK-801 stimulated grooming at 0.03, 0.1 and 1 mg/kg with maximal effects at the highest dose between 40 and 60 minutes. In contrast, MK-801 decreased grooming at 0.3 mg/kg between 20 and 30 minutes without further changes as compared with vehicle controls.

Fig. 5

Figure 5: Duration of eating. Ketamine had biphasic effects with an initial decrease of eating followed by rebound stimulation at the end of the test at 3 and 10 mg/kg. In contrast, ketamine had purely inhibitory effects on eating at 30 and 60 mg/kg.

Fig. 6

Figure 6: Duration of drinking. MK-801 increased drinking at 0.03 between 30 and 70 minutes and at 0.1 mg/kg between 100 and 110 minutes.

SUMMARY AND CONCLUSION

The present data illustrate the capacity of LABORAS™ to measure the effects of different test substances on motor and non-motor behaviors.

Advantages of this method of behavioral profiling include automation and the collection of different behavioral data within a single experimental context.

At high doses, the substances could not be differentiated based on their behavioral profile, although kinetics of effect differed for some substances.

At low doses, cocaine increased grooming whereas MK-801 and ketamine stimulated eating and drinking ,in contrast with their effects at high doses.

Comprehensive measurement of motor and non-motor behaviors using LABORAS™ allows comparison of the basic behavioral profile of a substance early in development with the profile of substances with known abuse liability.

Similarities of behavioral profile may be an indication to rapidly evaluate a new substance for abuse liability in more specific tests such as self-administration.

Porsolt □ 9 bis, rue Henri Martin, 92100 Boulogne-Billancourt, France □ Telephone +33 1 46 10 99 90 Fax +33 1 46 10 99 99

FOR MORE INFORMATION: dvirley@porsolt.com