How reinforcing is bupropion? Comparison with methylphenidate and cocaine by intravenous self-administration in rats

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INTRODUCTION

Bupropion is a relatively weak, selective dopamine reuptake inhibitor (Hyttel, 1982) that is used clinically to treat nicotine dependence. Bupropion is not a controlled drug (CD), but a number of case reports of bupropion abuse have appeared (McCormick, 2002; Baribeau & Araki, 2013; Oppek et al, 2014) and there is increasing evidence that this drug is abused by insufflation and intravenous injection (Stall et al, 2014; Lewis et al, 2014; Steele et al, 2016; Stassinos & Klein-Schwartz, 2016).

There are relatively few published studies describing the reinforcing effects of bupropion in animals and none to our knowledge that have systematically explored its reinforcing properties in rats. Therefore, we have investigated the reinforcing properties of bupropion compared with methylphenidate and cocaine (both C-II CDs) in an intravenous self-administration (IVSA) experiment.

METHODS

Mildly food-restricted, male, Sprague-Dawley rats were initially trained to lever-press for food rewards before being surgically implanted with in-dwelling jugular catheters. Rats were allowed to self-administer cocaine (0.36 mg/kg/injection [inj]) on a fixed ratio (FR5) schedule of reinforcement in 2hr training sessions. After establishment of consistent cocaine self-administration, the rats were subjected to saline extinction. The reinforcing effects of bupropion (0.03, 0.1 or 0.30 mg/kg/inj [Group 1]) and methylphenidate (0.01, 0.03 or 0.10 mg/kg/inj [Group 2]) were then evaluated on a FR5 reinforcement schedule in 2hr sessions. Intake was limited during acquisition, extinction and testing to 20 inj/session.
Results are presented as mean ± SEM (n = 6 rats/group).

CONCLUSIONS

- Bupropion served as a surprisingly strong, positive reinforcer in cocaine-maintained rats across a 10-fold dose range.
- Bupropion maintained self-administration levels on FR5 identical to the C-II stimulants, methylphenidate and cocaine.
- Further investigation of bupropion's relative reinforcing effect by break-point determination on a progressive ratio schedule is required to confirm and extend this finding.

REFERENCES

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Oppek K et al (2014) J Addict Med 8: 290-3.
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Figure 1: The reinforcing effects of bupropion on a FR5 schedule of reinforcement compared with cocaine and saline (A) and cumulative drug intake (B)

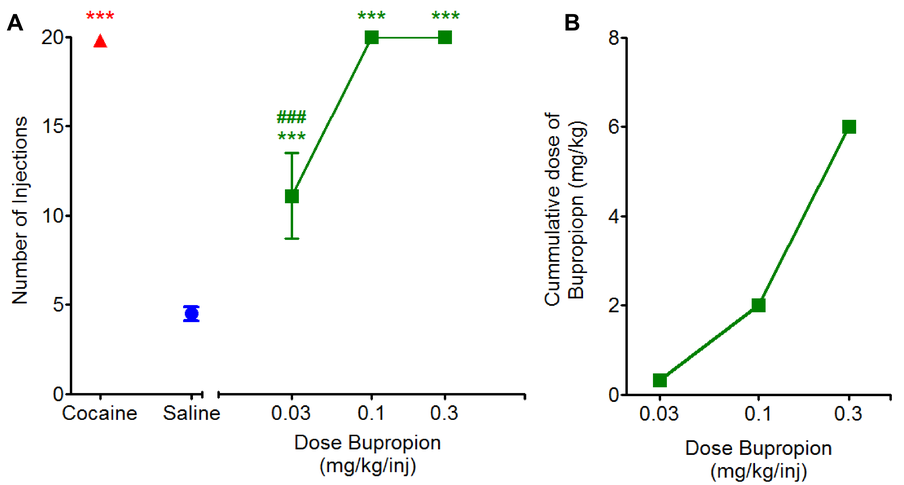
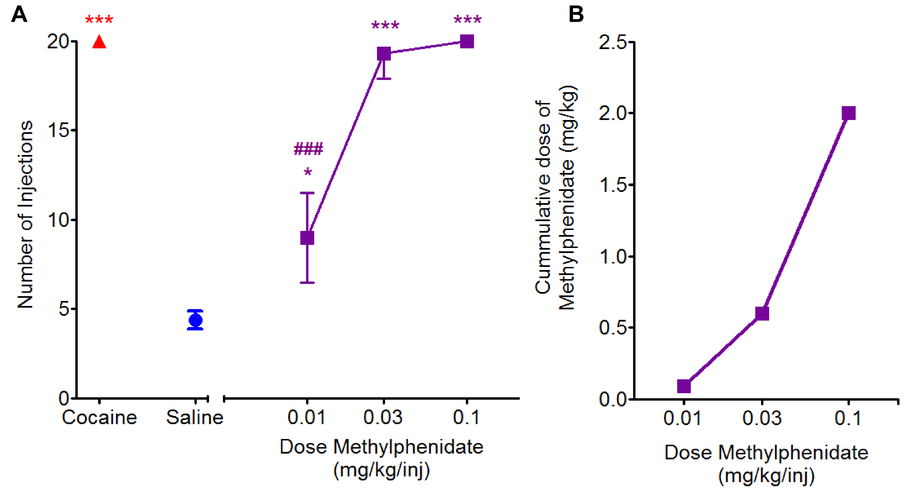


Figure 2: The reinforcing effects of methylphenidate on a FR5 schedule of reinforcement compared with cocaine and saline (A) and cumulative drug intake (B)



Drugs were evaluated in groups of 6 rats. Significantly different from saline *p<0.05, ***p<0.001. Significantly different from cocaine ### p<0.001.

RESULTS

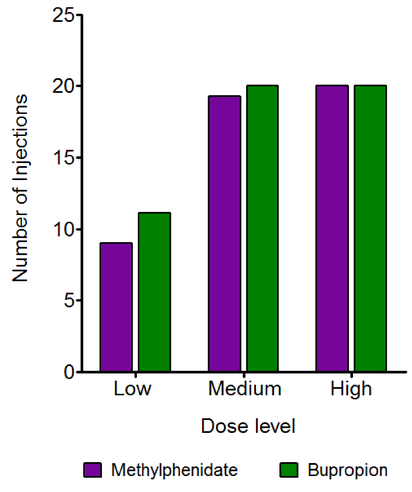
Figures 1 and 2: Cocaine maintained self-administration in the groups of rats used to evaluate bupropion [Group 1] and methylphenidate [Group 2] at levels significantly greater (p<0.001) than saline. There were no differences between Group 1 and Group 2 for the rates of either cocaine self-administration (19.8 ± 0.1inj/session, n = 10 [Group 1]; 20.0 ± 0.1inj/session, n = 10 [Group 2]) or saline extinction (4.5 ± 0.4 inj/session [Group 1]; 4.4 ± 0.5 inj/session, [Group 2]).

Figure 1: Methylphenidate (0.01, 0.03 or 0.10 mg/kg/inj) was dose-dependently self-administered by cocaine-trained rats at levels that were significantly (0.05 > p < 0.001) greater than saline. At the two highest doses, almost all of the rats took the maximum number of injections allowed according to the protocol.

Figure 2: Bupropion (0.03, 0.1 or 0.3 mg/kg/inj) dose-dependently maintained self-administration at levels significantly (p<0.001) greater than saline. All of the rats took the maximum number of injections of the two highest doses of bupropion.

Figures 1, 2 and 3: The levels of self-administration of bupropion were essentially identical to those maintained by of methylphenidate.

Figure 3: Comparison of the reinforcing profiles of methylphenidate and bupropion



Methylphenidate: 0.01 [Low dose]; 0.03 [Medium dose]; 0.1 mg/kg/inj [High dose]

Bupropion: 0.03 [Low dose]; 0.1 [Medium dose]; 0.3 mg/kg/inj [High dose]