An investigation of the reinforcing potential of Blue-181 in rats trained to self-administer heroin

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INTRODUCTION

Blue-181 is a non-narcotic, small molecule that is a selective agonist of μ/κ-opioid receptor heteromers. Blue-181 is being developed as an analgesic that will be devoid of the serious side-effects associated with the use of opioid painkillers. One of the most important of these problems is addictive potential.

To investigate the possible reinforcing (rewarding) effects of Blue-181, we determined whether it would maintain self-administration in rats that had been trained to self-administer heroin intravenously (i.v.). Heroin was selected as the positive control as it is a μ-opioid agonist and a Schedule 2 controlled drug (C-II). Saline was the non-reinforcing control. Butorphanol, which is a mixed μ/κ-opioid receptor partial agonist, was the reference comparator. Butorphanol was selected because it has low potential for human abuse and is a C-IV controlled drug in the USA.

METHOD

Male, Sprague-Dawley rats (200-225g; Charles River, UK) were mildly food restricted and trained to lever-press for food pellets on a fixed ratio (FR) 3 schedule of reward. They were implanted with jugular vein catheters and allowed to lever-press for heroin (15 μg/kg/injection[inj]) on a FR5 schedule in 2hr test sessions. After saline extinction, rats were divided into 2 groups to test Blue-181 (0.3, 1, 3 and 10 μg/kg/inj) or butorphanol (3, 10 and 30 μg/kg/inj) on FR5 schedule. The relative reinforcing effects of Blue-181, butorphanol and heroin were also compared by determining the break-points for reinforcement on a progressive ratio (PR) schedule. Drug doses are expressed as base equivalents. Results are mean ± sem, 7-8 rats/group.

Figure 1: Evaluation of the possible reinforcing effects of Blue-181 on a FR5 reinforcement schedule in heroin-trained rats

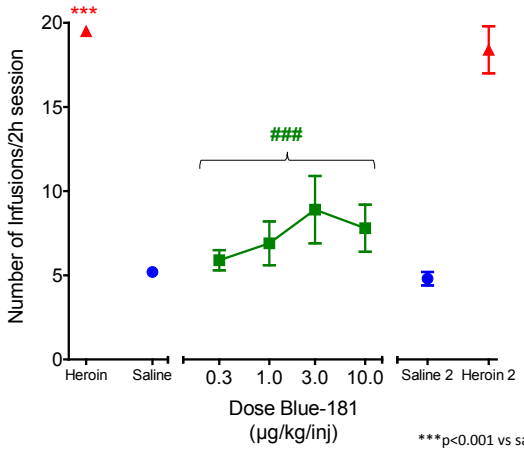
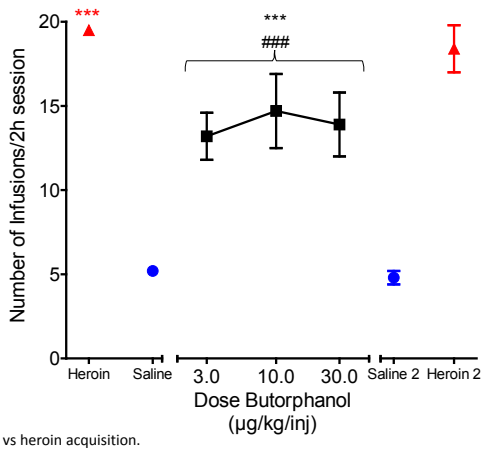
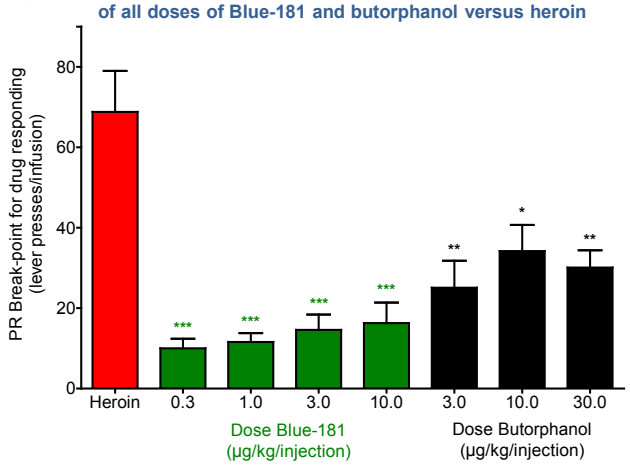


Figure 2: Evaluation of the reinforcing effects of butorphanol on a FR5 reinforcement schedule in heroin-trained rats



***p<0.001 vs saline extinction; ###p<0.001 vs heroin acquisition.

Figure 3: PR break-points to determine the relative reinforcing effect of all doses of Blue-181 and butorphanol versus heroin



n = 7-8/group. Dunnett's test: *p<0.05, **p<0.01, ***p<0.001 vs. heroin.

Table 1: Cumulative intake of Blue-181 and butorphanol on a FR5 reinforcement schedule in heroin-trained rats

Treatment	Testing dose (μg/kg/inj)	n	Cumulative drug intake (μg/kg i.v.) Mean	SEM	p value		
Blue-181	0.3 μg/kg/inj	8	2.0	0.0			
Blue-181	1 μg/kg/inj	8	8.0	1.0	***		
Blue-181	3 μg/kg/inj	8	26.0	5.0	***	###	
Blue-181	10 μg/kg/inj	8	80.0	12.0	***	###	†††
Butorphanol	3 μg/kg/inj	8	41.0	5.0			
Butorphanol	10 μg/kg/inj	8	135.0	23.0	§§§		
Butorphanol	30 μg/kg/inj	7	369.0	50.0	§§§	ΨΨΨ	

Blue-181: ***p<0.001 ***vs*** 0.3 μg/kg/inj; ###p<0.001 ***vs*** 1.0 μg/kg/inj; †††p<0.001 ***vs*** 3.0 μg/kg/inj.
Butorphanol: §§§ p<0.001 ***vs*** 3.0 μg/kg/inj; ΨΨΨ p<0.001 ***vs*** 10 μg/kg/inj.

RESULTS

- Figures 1 and 2: Heroin maintained robust FR5 self-administration in rats compared with the non-reinforcer, saline.
- Figure 1: None of the doses of Blue-181 were positively reinforcing on a FR5 schedule of reinforcement (mean inj/session = 5.9±0.6, 6.9±1.3, 8.9±2.0 and 7.8±1.4 for 0.3, 1, 3 and 10 μg/kg/inj, respectively; not significantly different from saline). The mean injections/session of all doses of Blue-181 were significantly lower than heroin (p<0.001) and butorphanol (p<0.05-p<0.001; not shown in Figure 1).
- Figure 2: All doses of butorphanol were positively reinforcing on the FR5 schedule when compared against saline.
- Table 1: There were incremental increases in the cumulative intake of Blue-181 and butorphanol as the unit doses were increased.
- Figure 3: The break-point for heroin reinforcement on PR testing was 68.8±10.2 lever-presses/inj [n=28]. The break-points for self-administration of butorphanol (3, 10 and 30μg/kg/inj), were all lower (p<0.05-p<0.001) than the break-point for heroin.
- Figure 3: Break-points for self-administration of Blue-181 (0.3, 1, 3 and 10 μg/kg/inj) were 10.0±2.4 [n = 8], 11.6±2.2 [n = 8], 14.6±3.8 [n = 8], and 16.3±5.1 [n = 8] lever presses/inj, respectively, and were all significantly lower (p<0.001) than heroin. The break-points for Blue-181 self-administration are very similar to our previously determined break-point for saline, 10.4 ± 0.8 [n = 31] lever-presses/inj (Heal et al, 2018).

CONCLUSIONS

- Heroin and butorphanol were positively reinforcing on a FR5 schedule, but butorphanol was less reinforcing than heroin on the PR schedule.
- Blue-181 did not serve as a reinforcer in heroin-maintained rats. Given the good predictive validity of the model, the results indicate Blue-181 will lack abuse potential in humans.

REFERENCES

Heal DJ, Gosden J, Smith SL (2018). Evaluating the abuse potential of psychedelic drugs as part of the safety pharmacology assessment for medical use in humans. Neuropharmacology, 142 (November), 89-115.

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