Oral vs. Intraperitoneal Dosing in the Rat Drug Discrimination Model

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INTRODUCTION

The regulatory agencies guidance for the assessment of abuse liability in preclinical models recommend using preferably the clinical route of administration although different routes may be considered depending on the model used and the context of non-medical use.
For the drug discrimination the routes of administration with fast onset of action, such as intraperitoneal (IP) or subcutaneous (SC) injection, are largely used. The present study aimed at investigating the effects of some drugs of abuse given through different routes of administration in a two choice drug discrimination operant task.

METHODS

The Training

- Study 1: 12 male Sprague Dawley rats were trained to discriminate cocaine (COC) at 10 mg/kg from its vehicle (VEH), given IP 10 minutes before the start of the session
- Study 2: 10 female Lister Hooded rats were trained to discriminate lorazepam (LZP) at 1 mg/kg from its VEH, given IP 60 minutes before the start of the session

Training

FR1→→→→→FR2→→→→→FR5→→→→→FR10

Right or Left Lever associated to Drug/VEH

CRITERIA FOR PROGRESSION

- >80% of the total session responses on the active lever
- at FR10 <5 incorrect lever presses up to the delivery of the first reinforcement

The Generalization Testing

Testing 1

Testing Drug was given IP

Testing 2

Testing Drug was given IP

- During generalization session both levers were actively delivering a pellet upon 10 consecutive lever presses on one of the two levers
- Study 1: rats received COC 1, 3, 10 mg/kg or VEH given IP (Testing 1; Figure 1A and Table 1A) at -10min; then COC 8, 16, 32 mg/kg or VEH given orally (PO; Testing 2, Figure 1B and Table 1B) at -60min
- Study 2: rats received LZP 0.1, 0.2, 0.5, 1 mg/kg or VEH given IP (Testing 1; Figure 2A and Table 2A) at -60min; then LZP 0.5, 1 and 3 mg/kg or VEH given PO (Testing 2; Figure 2B and Table 1B) at -60 min

DISCUSSION AND CONCLUSIONS

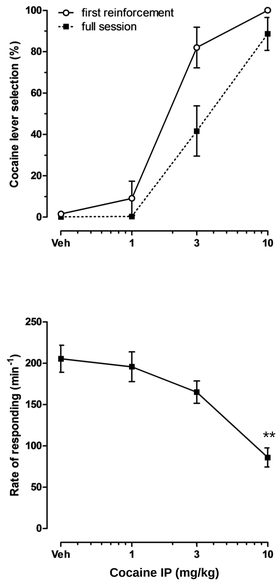
- The different routes of administration used for the training or generalization testing do not affect the robustness of the discriminative stimulus effect
- The choice of the route of administration is not critical as long as testing is conducted at T_{max} of the test item
- The oral route, which is often the proposed therapeutic route, can be suitable for drug discrimination studies despite the route used for the training drug
- However the possibility of production of different active metabolites depending on the route of administration used needs be taken in account

RESULTS

Study 1

Cocaine IP

1A



Cocaine PO

1B

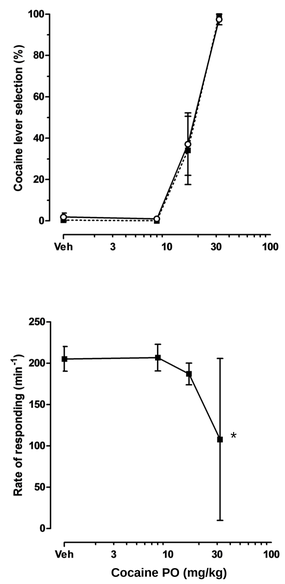


Figure 1. Generalization Testing: Effect of Cocaine.
Right panels (1A): cocaine was given IP; left panels (1B): cocaine was given PO.
Upper panels show percentages of selection of the lever associated to cocaine during the full session or up to the achievement of the first reinforcement. Lower panel show the rate of responding (i.e. total lever presses/min). *= P<0.05, **=P<0.01 vs VEH, Dunnett's test.
Full generalization (>80% responding on training drug-associated lever) was observed after treatment with 10 mg/kg IP and 32 mg/kg PO; partial generalization (between 20 and 80% responding on drug-associated lever) at 3 and 16 mg/kg IP and PO, respectively; no generalization (<20% responding on drug-associated lever) at 1 and 8 mg/kg.

Treatment	Subject	COC-associated Lever Presses Full session	VEH-associated Lever Presses Full session	Number of Reinforcements	COC-associated Lever Presses up to 1st Reinforcement	VEH-associated Lever Presses up to 1st Reinforcement
Vehicle 1 mL/kg IP	Z1	0	1000	100	0	10
	Z10	0	1000	100	0	10
	Z11	2	1000	100	1	10
	Z12	13	990	100	1	10
	Z2	0	1000	100	0	10
	Z3	0	1000	100	0	10
	Z4	0	1000	100	0	10
	Z5	0	1000	100	0	10
	Z6	0	1000	100	0	10
	Z7	0	1000	100	0	10
	Z8	1	1000	100	0	10
	Z9	3	1000	100	0	10
COC 1 mg/kg IP	Z1	4	1002	100	0	10
	Z10	0	1000	100	0	10
	Z11	0	1000	100	0	10
	Z12	22	996	100	0	10
	Z2	0	1000	100	0	10
	Z3	0	1000	100	0	10
	Z4	2	1000	100	0	10
	Z5	0	1000	100	0	10
	Z6	1	1000	100	0	10
	Z7	0	1000	100	0	10
	Z8	10	990	100	10	0
	Z9	1	1000	100	1	10
COC 3 mg/kg IP	Z1	1000	1	100	10	1
	Z10	0	1000	100	0	10
	Z11	35	999	100	34	8
	Z12	1007	4	100	10	0
	Z2	233	770	100	10	0
	Z3	184	837	100	10	0
	Z4	650	357	100	10	0
	Z5	990	10	100	10	0
	Z6	749	261	100	10	1
	Z7	90	912	100	10	0
	Z8	82	920	100	10	0
	Z9	9	1001	100	3	11
COC 10 mg/kg IP	Z1	1000	3	100	10	0
	Z10	1000	1	100	10	0
	Z11	1000	5	100	10	0
	Z12	430	0	43	10	0
	Z2	128	882	100	10	0
	Z3	400	370	77	10	0
	Z4	1000	0	100	10	0
	Z5	1000	0	100	10	0
	Z6	947	3	94	10	0
	Z7	1000	0	100	10	0
	Z8	908	0	90	10	0
	Z9	871	2	87	10	0

Table 1A. Generalization Testing: Effect of Cocaine following IP administration

Treatment	Subject	COC-associated Lever Presses Full session	VEH-associated Lever Presses Full session	Number of Reinforcements	COC-associated Lever Presses up to 1st Reinforcement	VEH-associated Lever Presses up to 1st Reinforcement
Vehicle 5 mL/kg PO	Z1	12	990	100	2	10
	Z10	0	1000	100	0	10
	Z11	0	1000	100	0	10
	Z12	11	990	100	0	10
	Z4	0	1000	100	0	10
	Z5	0	1000	100	0	10
	Z7	0	1000	100	0	10
	Z8	0	1000	100	0	10
	Z9	1	1000	100	0	10
COC 8 mg/kg PO	Z1	0	990	100	0	10
	Z10	0	1000	100	0	10
	Z11	1	1000	100	0	10
	Z12	0	990	100	0	10
	Z4	0	1000	100	0	10
	Z5	0	1000	100	0	10
	Z7	0	1000	100	0	10
	Z8	0	1000	100	0	10
	Z9	0	1000	100	0	10
COC 16 mg/kg PO	Z1	4	1000	100	4	10
	Z10	61	940	100	1	10
	Z11	1005	2	100	15	2
	Z12	1000	0	100	10	0
	Z4	0	1000	100	0	10
	Z5	1000	0	100	10	0
	Z7	0	1000	100	0	10
	Z8	0	1000	100	0	10
	Z9	2	1000	100	2	10
COC 32 mg/kg PO	Z1	1000	0	100	10	0
	Z10	1000	2	100	10	0
	Z11	880	8	88	10	0
	Z12	300	0	30	10	0
	Z4	1000	0	100	10	0
	Z5	1000	0	100	10	0
	Z7	1000	11	100	10	3
	Z8	590	44	63	10	0
	Z9	400	0	40	10	0

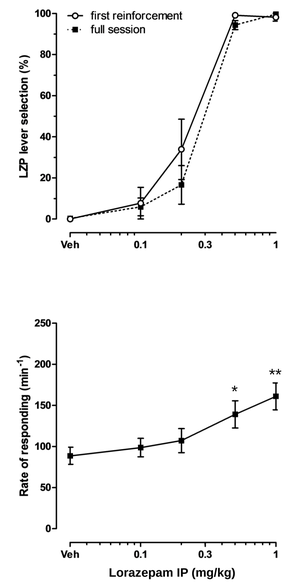
Table 1B. Generalization Testing: Effect of Cocaine following PO administration

Number of presses on the COC- and VEH-associated levers during the full session and up to the achievement of the first reinforcement. Number of reinforcements gained are also reported.

Study 2

LZP IP

2A



LZP PO

2B

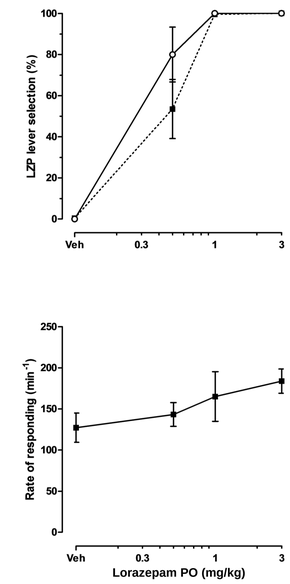


Figure 2. Generalization Testing: Effect of Lorazepam.
Right panels (2A): lorazepam was given IP; left panels (2B): lorazepam was given PO.
Upper panels show percentages of selection of the lever associated to lorazepam during the full session or up to the achievement of the first reinforcement. Lower panel show the rate of responding (i.e. total lever presses/min). *= P<0.05, **=P<0.01 vs VEH, Dunnett's test.
Full generalization was observed following dosing with LZP at 0.5 and 1 mg/kg IP and all the doses tested with LZP given PO; no generalization at 0.1 and 0.2 mg/kg IP.

Treatment	Subject	LZP-associated Lever Presses Full session	VEH-associated Lever Presses Full session	Number of Reinforcements	LZP-associated Lever Presses up to 1st Reinforcement	VEH-associated Lever Presses up to 1st Reinforcement
Vehicle 1 mL/kg IP	F1	5	590	58	0	10
	F10	10	972	98	0	10
	F2	0	1000	100	0	10
	F3	2	1000	100	0	10
	F4	1	860	86	0	10
	F5	0	1000	100	0	10
	F6	7	920	92	0	10
	F7	0	1000	100	0	10
	F8	2	1000	100	0	10
	F9	1	1000	100	0	10
LZP 0.1 mg/kg IP	F1	3	972	97	0	10
	F10	0	1000	100	0	10
	F2	1	1000	100	0	10
	F3	4	934	93	0	10
	F4	110	820	93	0	10
	F5	1	1000	88	0	10
	F6	9	880	100	0	10
	F7	13	1001	100	0	10
	F8	430	573	100	10	3
	F9	9	1000	100	0	10
LZP 0.2 mg/kg IP	F1	12	830	83	0	10
	F10	3	1000	100	0	10
	F2	1	1000	100	0	10
	F3	3	1000	100	0	10
	F4	7	891	89	5	11
	F5	33	970	100	10	0
	F6	640	360	100	0	10
	F7	96	582	67	10	0
	F8	810	199	100	10	0
	F9	10	1002	100	1	12
LZP 0.5 mg/kg IP	F1	570	107	64	10	1
	F10	1000	0	100	10	0
	F2	840	180	100	10	0
	F3	1000	1	100	10	0
	F4	1000	0	100	10	0
	F5	1000	3	100	10	0
	F6	930	70	100	10	0
	F7	971	49	100	10	0
	F8	1002	3	100	10	0
	F9	901	111	100	10	0
LZP 1 mg/kg IP	F1	990	24	100	10	0
	F10	1000	0	100	10	0
	F2	1000	2	100	10	0
	F3	1000	0	100	10	0
	F4	1000	0	100	10	0
	F5	1000	0	100	10	0
	F6	1000	3	100	10	0
	F7	1000	0	100	10	0
	F8	1001	0	100	10	0
	F9	875	9	86	25	6

Table 2A. Generalization Testing: Effect of Lorazepam following IP administration

Treatment	Subject	LZP-associated Lever Presses Full session	VEH-associated Lever Presses Full session	Number of Reinforcements	LZP-associated Lever Presses up to 1st Reinforcement	VEH-associated Lever Presses up to 1st Reinforcement
Vehicle 5 mL/kg PO	F1	17	741	74	0	10
	F10	0	1000	100	0	10
	F2	0	1000	100	0	10
	F3	1	1000	100	0	10
	F4	5	942	94	0	10
	F5	0	1000	100	0	10
	F6	9	670	67	0	10
	F7	0	1000	100	0	10
	F8	1	1000	100	0	10
	F9	0	1000	100	0	10
LZP 0.5 mg/kg PO	F1	750	58	78	0	10
	F10	1001	13	100	10	0
	F2	1000	10	100	10	0
	F3	11	990	100	10	0
	F4	1000	1	100	10	0
	F5	1000	0	100	10	0
	F6	715	291	100	10	0
	F7	1000	10	100	10	0
	F8	500	507	100	0	10
	F9	72	930	100	10	0
LZP 1 mg/kg PO	F1	692	10	69	10	0
	F10	1001	0	100	10	0
	F2	1000	17	100	10	0
	F3	1000	0	100	10	0
	F4	1000	0	100	10	0
	F5	1000	9	100	10	0
	F6	1002	0	100	10	0
	F7	460	0	46	10	0
	F8	1000	1	100	10	0
	F9	780	0	78	10	0
LZP 3 mg/kg PO	F1	1000	2	100	10	0
	F10	1000	0	100	10	0
	F2	1000	0	100	10	0
	F3	1000	0	100	10	0
	F4	1000	0	100	10	0
	F5	1000	0	100	10	0
	F6	1000	0	100	10	0
	F7	1000	0	100	10	0
	F8	1000	0	100	10	0
	F9	1001	0	100	10	0

Table 2B. Generalization Testing: Effect of Lorazepam following PO administration

Number of presses on the LZP- and VEH-associated levers during the full session and up to the achievement of the first reinforcement. Number of reinforcements gained are also reported.