NeuroDetective® International

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SAMPLE FINAL REPORT

Self-Administration Study

Date :

Introduction

This study tested the addictive potential of **Company's** compound, denominated "XX" throughout this report. The technique used was intravenous self-administration.

Intravenous self-administration is one of the major behavioural tests used in rodents to predict the addictive potential of a test compound. For example drugs of abuse can maintain an operant response by the subject animal when reinforced by intravenous delivery. Several schedules and variation of the self-administration paradigm can be used to estimate the abuse potential of a drug. Acquisition of responding at low fixed ratios of drug intravenous

self-administration permits estimation of the reinforcing properties of a test compound (Yokel, 1987). The strength of these reinforcing properties can then be estimated by increasing the response requirement to obtain the drug (for review, Richardson and Roberts, 1996; Stafford *et al.*, 1998). By this approach it is possible to discern for example that, while a certain drug may be reinforcing, the subject animal maintains intravenous self-administration only at low ratio requirements, suggesting a low addictive potential (Marinelli *et al.*, 1998). Furthermore addictive drugs that share common neurochemical substrates can substitute for one another in the self-administration paradigms, especially if they are from the same class. Thus, a non-contingent administration of a test psychostimulant will increase the reinforcing effects of a second, known psychostimulant, resulting in the animal actually decreasing self-administration of the second drug in an effort to maintain a constant level of reinforcement (Koob and Bloom, 1988).

In this study we compared intravenous self-administration of the XX compound to self-administration of cocaine. Animals were first trained using an FR1 schedule, then a progressive ratio schedule was applied. Finally we analysed the effect of the injection of the XX compound on cocaine self-administration.

I. Methods.

1. Subjects:

Forty-eight male Sprague-Dawley rats weighing 400-450g were used. As they arrived in the laboratory, they were placed in individual cages. Light-dark cycle (8.00h off, 20.00h on), temperature (21°C ± 2) and humidity

(60 ± 5%) were all controlled and kept constant. Surgery was performed following a 15-day habituation period, duting which the animals were handled daily.

2. Drugs:

Cocaine HCl (SIGMA) and "XX" (supplied by COMPANY) were dissolved in NaCl 0.9%.

3. Catheter fabrication:

Guide-cannulae (C313G 5UP, Plastics One, Roanoke, Virginia, USA), silastic tubing (0.3 mm int. diam, 0.64 mm ext. diam, Dow Corning, Midland, Texas, USA), dental cement, silicone gum, and plastic mesh (Plastics One, Roanoke, Viriginia, USA) were used in catheter manufacture, which was standardized by use of a special aluminium mould.

4. Surgery:

Under ketamine anaesthesia, a catheter (dead volume: 12 µl) was inserted in the right auricle through the jugular vein. The catheter was passed through the skin and fixed in the mid-scapular region. The catheter was filled with a heparinized solution (100 IU/ml). The catheter was flushed with the same heparinized solution after each self-administration session. Following surgery, an antibiotic treatment was applied during 4 days (gentamicine, 1 mg/kg i.p.).

5. Intravenous self-administration apparatus:

Sixteen self-administration boxes were used (Imétronic, Pessac, France). Each box (40 cm long x 30 cm wide x 35 cm high) had two holes in the middle of two opposite walls at 5 cm above the floor. Each box was

equipped with an infusion pump delivering the drug solution through a single channel swivel and tygon tube. The boxes were also equipped with two photoelectric cell beams for detection of horizontal locomotor activity. Experimental parameters and data recording were controlled by PC-compatible software (Imétronic, Pessac, France).

By introducing its nose into one of the two holes (the active hole), the rat broke a photocell beam which triggered the infusion pump to deliver the drug (20µl/sec). Each infusion was followed by a time-out period (40 sec) during which nose-pokes in the active hole were recorded but were without effect on the infusion pump. A nose-poke in the other hole (the inactive hole) was without scheduled consequence at any time. Number of active and inactive nose-pokes, number of infusions, and horizontal locomotor activity were all recorded over each self-administration session.

II. Procedures.

1. Acquisition of "XX" self-administration ~ comparison with cocaine:

Four groups of animals (n=12 per group) were each balanced for body weight [Group effect: F (3,44) = 0.14, p = 0.93; Group x Day interaction: F (9,132) = 0.29, p =0.97] (Figure 11), and time of drug self-administration (each group equally represented in each of the three daily self-administration sessions). One group was tested for cocaine self-administration (0.8 mg/kg/infusion), while the other three groups were tested for "XX" self-administration. Each of the latter were tested with one dose of the compound (0.25, 0.5 or 1 mg/kg/infusion).

Beginning five to six days after surgery to implant the catheters, rats were placed daily, for one hour, in the self-administration boxes. A fixed ratio 1 was first applied [FR1): a nose-poke into the active hole (outside of the time-out period) induced one drug infusion, as defined above. Animals were tested with this protocol during 9 daily sessions.

2. Between-session progressive ratio schedule:

Following the 9 days under FR1, a second step was initiated: the response requirement (ratio) needed to trigger infusion of the drug was progressively increased to FR8 (FR2, 1 session; FR3, 3 sessions; FR5, 4 sessions; FR8, 4 sessions).

3. Effect of an acute administration of "XX" and of amphetamine on cocaine self-administration:

Animals trained for cocaine self-administration were maintained on FR8. Then, according to a Latin square design, these animals were administered one of three different doses of "XX" (10, 30 or 100 mg/kg) or vehicle, i.p. Thirty minutes later the animals were tested for cocaine self-administration. One training session separated two test sessions. The results obtained in this experiment (see below) led us to test a dose of "XX" that was intermediate between 30 and 100 mg/kg., specifically 60 mg/kg. (or vehicle), using a Latin Square design as before. Also, the effects produced by the two highest doses of "XX" led us to compare them to those of an acute administration of amphetamine. Again according to a Latin square design conducted over two days, amphetamine (2.5 mg/kg) or vehicle was administered i.p. 20 min before a cocaine self-administration session.

4. Data analyses:

For all the data, a logarithmic transformation was applied in order to normalize the distributions (in the tables of individual data, results are expressed as non-normalized data.).

For all the experiments, repeated measures analysis of variance (ANOVA) was used. Depending on the experiment, Group (cocaine, XX0.25, XX0.5, XX1) was the between-subjects factor, while Treatment (Vehicle, XX10, XX30, XX100; or Vehicle, XX60; or Vehicle, Amphetamine), Hole status (active vs inactive), or Time (number of sessions or pre/post treatment) were within-subjects factors.

For the effect of an acute administration of "XX" on subsequent cocaine self-administration, self-administration performance during the test session (post-treatment) and during the training session immediately preceding the test session (pre-treatment) were compared. For the effect of an acute administration of amphetamine on cocaine self-administration, self-administration following vehicle administration was compared to self-administration following amphetamine administration.

Newmann-Keuls and simple main effects analyses were used to determine the locus of significant main effects and interactions. A significance level of $p<0.05$ was used for all statistical comparisons.

III. Results.

1. Acquisition of "XX" Self-administration ~ comparison with cocaine:

Rats readily learned to self-administer cocaine. Compared to the inactive hole, animals exhibited a progressively higher number of nose-pokes into the active (i.e., drug-administering) hole, F (8,72) = 2.25, p <

0.05, Session x Hole interaction. Furthermore, responding rate did not significantly differ from session 1 to 9, F (8,72) = 1.19, p = 0.31, Session main effect. Rats from the "XX" groups also showed a higher number of nose-pokes into the active hole, F (1,27) = 10.69, p < 0.01, Hole main effect. This effect was not dependent on the specific dose tested, F (2,27) = 1.81, p = 0.18, Hole x Group interaction. Contrary to the cocaine group but similarly across all three "XX" dose groups, nose poking into both holes progressively decreased over the 9 sessions, F (8,216) = 46.31, p <0.0001, Session main effect; F (8,216) = 1.34, p = 0.22, Session x Hole interaction; F (16,216) = 1.28, p = 0.21, Session x Hole x Group interaction. (See Figure 1.)

As expected from the low ratio used in acquisition, statistical analysis did not reveal differences among the four experimental groups for total responding over the first 9 sessions, F (3,33) = 1.57, p = 0.21, Group main effect. However, the four self-administration groups did differ significantly in the total number of self-infusions, F (3,33) = 5.62, p < 0.01, Group main effect (see Figure 2). Although the three "XX" groups did not differ from one another, they all exhibited a lower number of self-infusions than the cocaine group. The cocaine group showed a progressive increase in the number of self-infusions, F (8,48) = 2.24, p < 0.05, Session main effect. And at FR1 the number of cocaine self-administrations was stable over the last three sessions, F (2,12) = 2.67, p = 0.1, Session main effect. In contrast the three "XX" groups showed a progressive decrease in number of self-infusions over the 9 acquisition sessions, F (8,216) = 70.43, p < 0.0001, Session main effect; F (16,216) = 1.33, p = 0.17, Session x Group interaction.

2. Between-session progressive ratio schedule:

Increasing the number of nose-pokes required to obtain an infusion (i.e., progressively increasing the FR ratio) affected the groups differently, both in total number of responses made (F (3,33) = 21.62, $p < 0.0001$, Group main effect) and in total number of self-infusions (F (3,33) = 80.07, $p < 0.0001$, Group main effect). For the cocaine group, increasing the ratio produced an increase in active responding, F (11,66) = 2.16, $p < 0.03$, Session main effect; F (11,66) = 3.43, $p < 0.0001$, Session x Hole interaction (see Figure 1). In fact, for the cocaine group the number of self-infusions remained high and stable across sessions, F (14,84) = 1.42, $p = 0.16$, Session main effect (see Figure 2). In contrast, the three "XX" groups made fewer responses as the ratio increased, F (11,297) = 3.03, $p < 0.001$, Session main effect. This led to a further decrease in the number of self-infusions for the XX-receiving groups, which was true for all doses, F (14,378) = 22, $p < 0.0001$, Session main effect; F (28,378) = 0.86, $p = 0.66$, Session x Group interaction. (See Figure 2)

3. Effect of an acute administration of "XX" and of amphetamine on cocaine self-administration:

"XX", administered 30 minutes before the cocaine self-administration session, reduced post-treatment responses to cocaine, both in terms of number of nose-pokes into the active hole, and total cocaine self-administered (number of infusions). However this effect was restricted to one dose of "XX," 100mg/kg. Statistical analyses showed an overall effect of pre-treatment with "XX" on nose—pokes (Figure 3) [F (3,18) = 5.08, $p < 0.03$, Dose x Time interaction], as well as on cocaine intake (Figure 4) [F (1,6) = 39.05, $p < 0.001$], Time main effect; F (3,18) = 18.31, $p < 0.0001$, Dose main effect; F (3,18) = 23, $p < 0.0001$, Dose x Time interaction]. Responses to the active hole were the obly ones affected, F (3,18) = 5.3, $p < 0.01$, Dose effect, Active hole; F

(3,18) = 0.34, p = 0.79, Dose effect, Inactive hole. As is evident from both Figures 3 and 4, these effects are all due to the 100 mg/kg dose. Interestingly, this effect was associated with a decrease in locomotor activity (Figure 5). A post-hoc analysis revealed that "XX" 100 mg/kg produced a significant decrease in locomotor activity (p < 0.01) as compared to the pre-treatment (baseline) condition.

The 60 mg/kg dose produced a significant decrease in both the number of self-infusions (Figure 7) [F (1,4) =115,74, p <0.001, Dose effect] and the number of active responses [F (1,4) = 13.99, p < 0.05, Dose effect] without altering inactive responding (Figure 6) [F (1,4) = 0.44, p = 0.54, Dose effect]. This effect on cocaine intake was also associated with a decrease in locomotor activity (Figure 8) [F (1,4) = 26.63, p <0.01, Dose effect].

Compared to vehicle, amphetamine (2.5 mg/kg) produced a significant decrease in both the number of active nose-pokes [F (1,5) = 27.88, p < 0.01, Dose effect; F (1,5) = 19.43, p < 0.01, Dose x Hole interaction], as well as in the number of self-infusions [F (1,5) = 7.5, p < 0.05, Dose effect]. See Figure 9. Inactive responding was not affected and locomotor activity was not altered (Figure 10) [F (1,5) = 1.56, p = 0.26, Dose effect].

IV. Conclusions

The present experiments show that, at the doses tested here and compared to cocaine, compound "XX" is not reinforcing in naive rats. In particular the XX compound fulfils none of the criteria used to demonstrate positive reinforcing effects of a test compound. First, independently from the response/reward ratio used, the number of nose-pokes into the active device and the number of self-infusions by XX –treated animals decreased

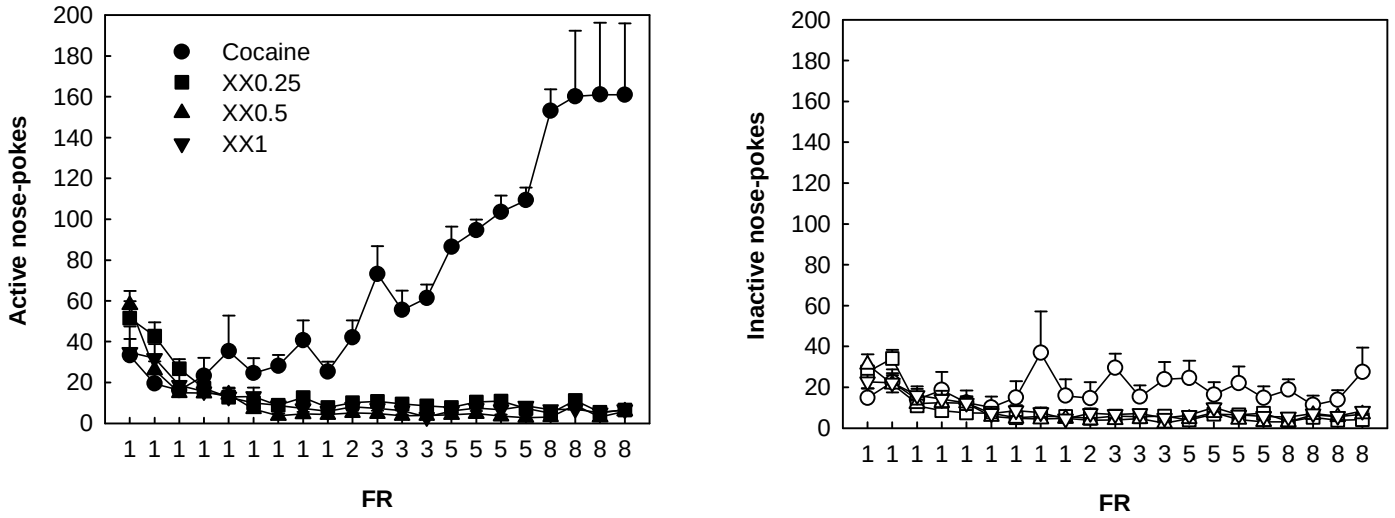
over the course of test sessions. Second, there was no dose /response effect of the XX compound. Third, responding for the XX compound was not sensitive to a change in FR ratio. In contrast, responding for cocaine progressively increased as the FR ratio increased, which resulted in a constant number of infusions over the test session.

The results of this study also show that acute injection of XX dose-dependently decreases responding for cocaine, an effect that was similar to the one observed with amphetamine. However, this decrease in responding for cocaine was paralleled by a decrease in locomotor activity, whilst amphetamine decreased responding without modifying locomotion. This observation raises the possibility that the decrease in responding for cocaine self-administration following XX treatment is secondary to a decrease in motor activity, and does not result from an interaction of the XX compound with the reinforcing effects of cocaine.

In order to examine this possibility two supplementary experiments will be needed. The first would examine place conditioning induced by the XX compound. This test assays whether the XX compound, in the range of doses that reduce responding for cocaine, has reinforcing properties on its own. The advantage of the place conditioning test in this case is that it is not influenced by any decrease in locomotion that may be induced by a test compound. The second experiment would test whether the XX compound can induce reinstatement of cocaine-induced behaviours in cocaine trained rats, and eventually substitute for cocaine.

Figures

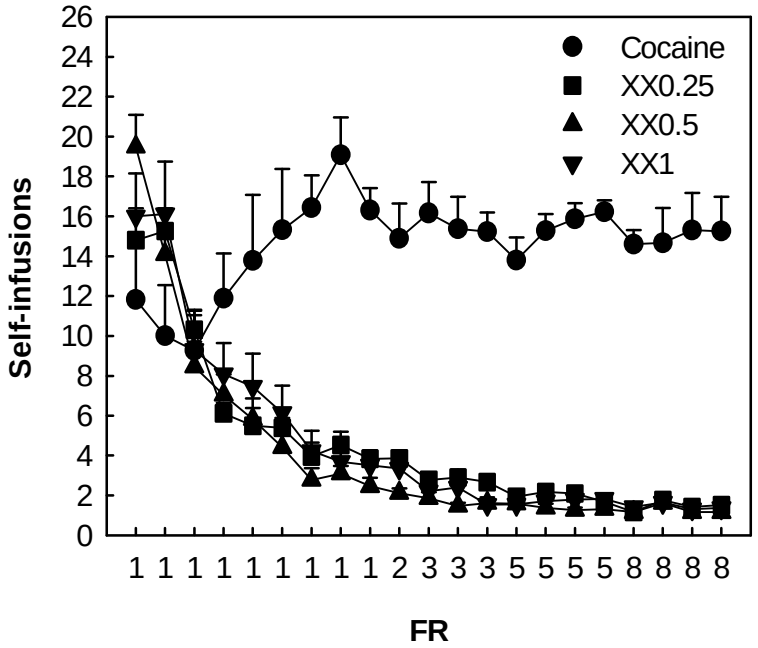
Figure 1: *Cocaine and "XX" self-administration ~ Responding in active and inactive holes.*



Mean ± SEM : Tables 1a, b, c, d
Tables 2a, b, c, d

Individual data :Tables I, Ibis
Tables II, IIbis

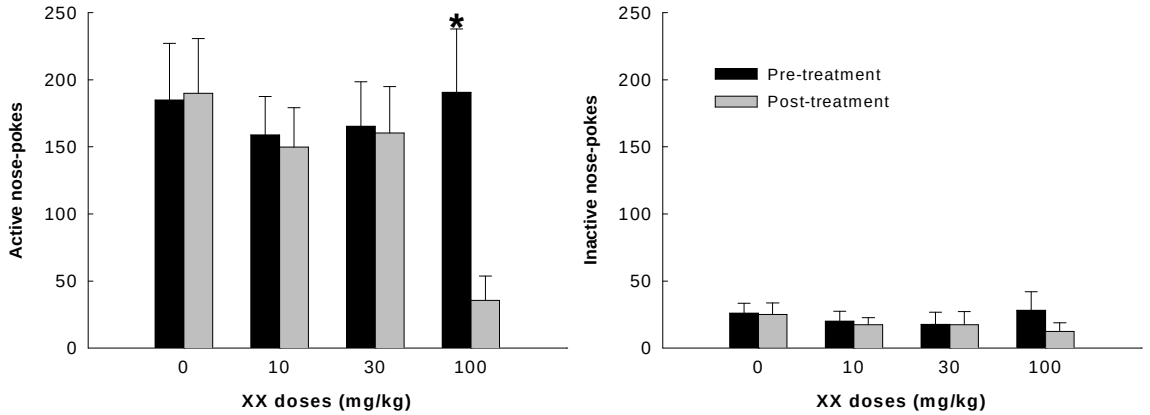
Figure 2: *Cocaine and "XX" self-administration ~ Self-infusions.*



Mean ± SEM : Tables 3a, b, c, d

Individual data :Tables III, IIIbis

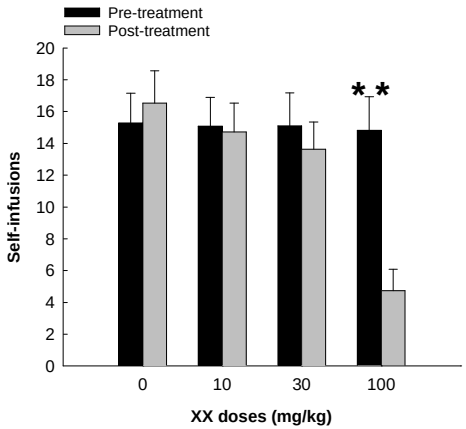
Figure 3: *Effect of "XX" (10, 30, 100 mg/kg) on cocaine self-administration ~ Responding in active and inactive holes.*



Mean ± SEM : Tables 4a, 4b

Individual data :Tables IVa, IVb

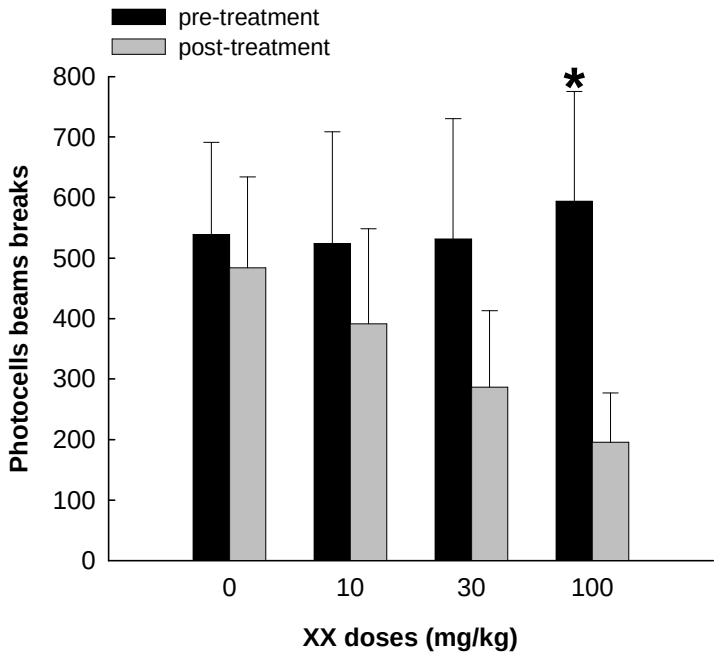
Figure 4: *Effect of "XX" (10, 30, 100 mg/kg) on cocaine self-administration ~ Self-infusions.*



Mean ± SEM : Table 5

Individual data :Table V

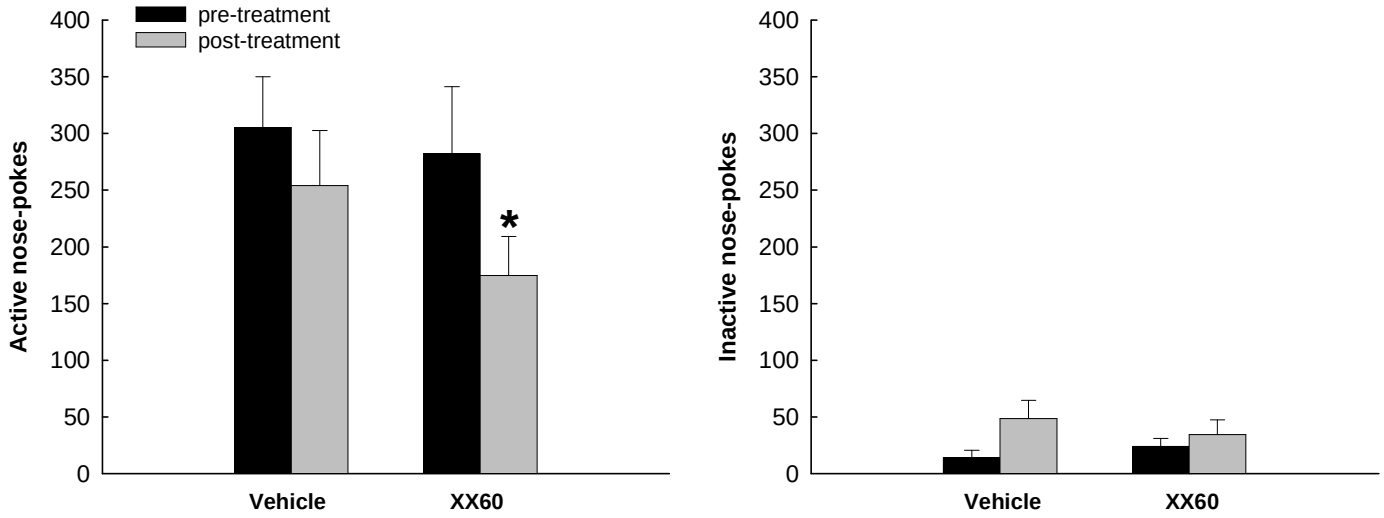
Figure 5: *Effect of "XX" (10, 30, 100 mg/kg) on cocaine self-administration ~ Locomotor activity.*



Mean ± SEM : Table 6

Individual data :Table VI

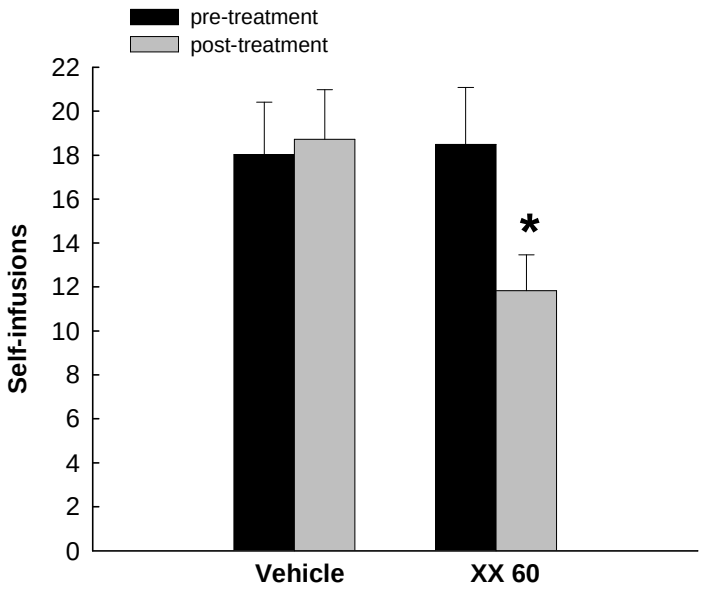
Figure 6: *Effect of "XX" (60 mg/kg) on cocaine self-administration ~ Responding in active and inactive holes.*



Mean ± SEM : Tables 7a, 7b

Individual data :Tables VIIa, VIIb

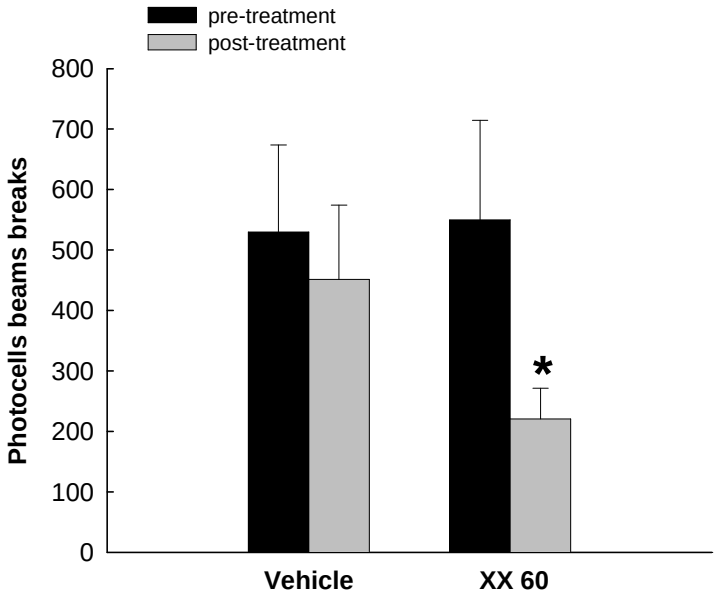
Figure 7: *Effect of "XX" (60 mg/kg) on cocaine self-administration ~ Self-infusions.*



Mean ± SEM : Table 8

Individual data :Table VIII

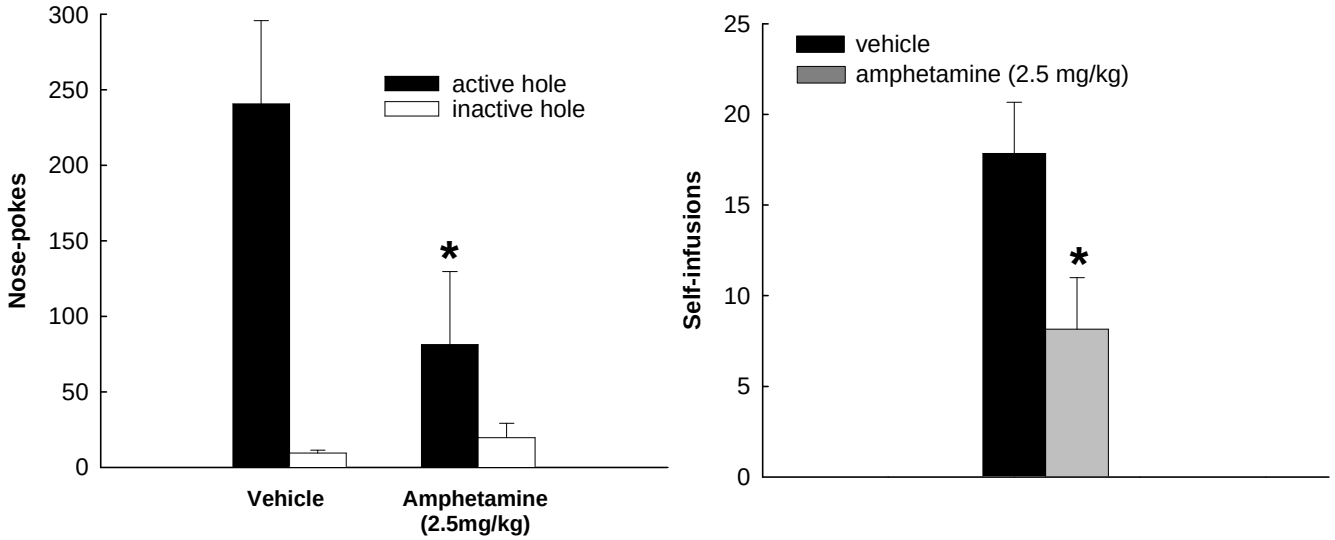
Figure 8: *Effect of "XX" (60 mg/kg) on cocaine self-administration ~ Locomotor activity.*



Mean ± SEM : Table 9

Individual data :Table IX

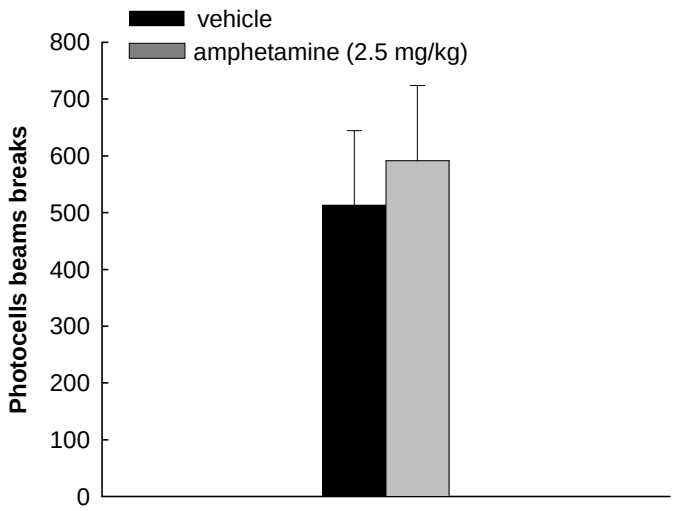
Figure 9: *Effect of amphetamine (2.5 mg/kg) on cocaine self-administration ~ Responding in active and inactive holes, self-infusions.*



Mean ± SEM : Table 10

Individual data :Table X

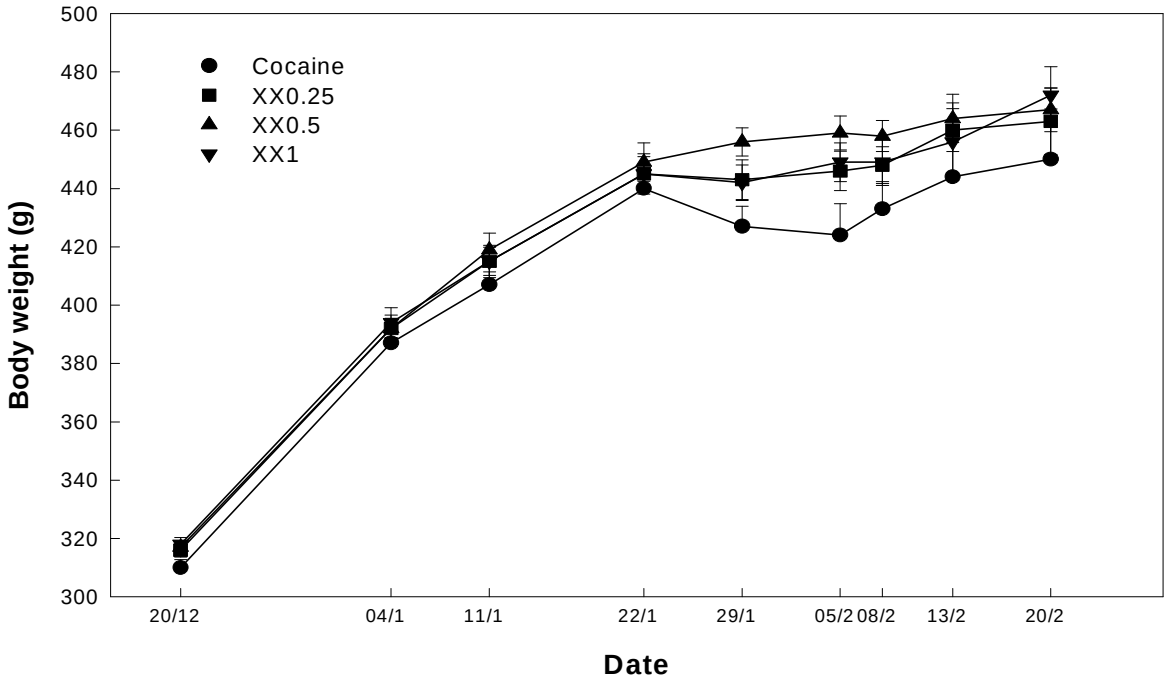
Figure 10: *Effect of amphetamine (2.5 mg/kg) on cocaine self-administration ~ Locomotor activity.*



Mean ± SEM : Table 11

Individual data :Table XI

Figure 11: *Rats' body weight.*



Mean ± SEM : Table 12

Individual data :Table XII, XIIbis

Tables

Table 1a

Cocaine self-administration

Active nose-pokes (Mean ± SEM)

(n=7)

Fixed Ratio	Mean	SEM
FR1	33.25	14.25
FR1	19.45	6.06
FR1	16.25	4.30
FR1	23.30	8.77
FR1	35.32	17.42
FR1	24.62	7.38
FR1	28.19	5.40
FR1	40.60	9.79
FR1	25.37	4.91
FR2	42.17	8.34
FR3	73.14	13.66
FR3	55.47	9.52
FR3	61.45	6.63
FR5	86.49	9.83
FR5	94.63	5.12
FR5	103.60	7.94
FR5	109.29	6.15
FR8	153.03	10.52
FR8	160.16	32.10
FR8	161.03	35.20
FR8	160.94	35.02

Table 2a

Cocaine self-administration

Inactive nose-pokes (Mean ± SEM)

(n=7)

Fixed Ratio	Mean	SEM
FR1	14.79	4.76
FR1	22.39	6.35
FR1	13.93	5.29
FR1	18.61	8.88
FR1	12.44	5.87
FR1	10.05	5.41
FR1	14.94	8.09
FR1	36.79	20.25
FR1	15.81	8.06
FR2	14.62	7.82
FR3	29.49	6.94
FR3	15.28	5.72
FR3	23.81	8.61
FR5	24.45	8.43
FR5	16.34	6.14
FR5	21.94	8.21
FR5	14.79	5.54
FR8	18.75	5.12
FR8	11.23	4.61
FR8	13.75	4.73
FR8	27.48	11.93

Table 3a

Cocaine self-administration

Self-Infusions (Mean ± SEM)

(n=7)

Fixed Ratio	Mean	SEM
FR1	11.81	2.96
FR1	10.01	2.54
FR1	9.26	1.78
FR1	11.88	2.26
FR1	13.77	3.31
FR1	15.32	3.06
FR1	16.43	1.63
FR1	19.08	1.88
FR1	16.31	1.10
FR2	14.88	1.77
FR3	16.17	1.55
FR3	15.38	1.61
FR3	15.23	0.97
FR5	13.80	1.15
FR5	15.27	0.84
FR5	15.87	0.80
FR5	16.22	0.59
FR8	14.60	0.70
FR8	14.67	1.74
FR8	15.30	1.87
FR8	15.25	1.73

Table 1b

XX0.25 self-administration

Active nose-pokes (Mean ± SEM)

(n=11)

Fixed Ratio	Mean	SEM
FR1	51.55	8.26
FR1	42.85	6.61
FR1	26.79	4.69
FR1	17.25	3.35
FR1	12.70	3.33
FR1	10.07	1.72
FR1	8.91	1.97
FR1	12.54	2.55
FR1	7.86	1.28
FR2	10.15	1.26
FR3	10.71	2.55
FR3	9.56	2.14
FR3	8.61	1.82
FR5	7.83	1.96
FR5	10.43	2.13
FR5	10.94	2.44
FR5	7.34	2.00
FR8	4.94	0.90
FR8	11.26	2.54
FR8	5.46	1.68
FR8	6.52	1.63

Table 2b

XX0.25 self-administration

Inactive nose-pokes (Mean ± SEM)

(n=11)

Fixed Ratio	Mean	SEM
FR1	27.51	2.84
FR1	34.08	4.21
FR1	10.92	2.22
FR1	8.52	1.75
FR1	7.40	1.53
FR1	7.20	1.70
FR1	5.13	1.14
FR1	5.75	1.28
FR1	5.63	0.85
FR2	4.70	1.27
FR3	5.90	0.79
FR3	5.49	1.15
FR3	5.81	1.35
FR5	3.93	1.04
FR5	6.73	1.81
FR5	6.37	1.26
FR5	7.26	1.36
FR8	3.15	0.70
FR8	5.23	1.37
FR8	3.89	1.11
FR8	4.16	0.80

Table 3b

XX0.25 self-administration

Infusions (Mean ± SEM)

(n=11)

Fixed Ratio	Mean	SEM
FR1	14.80	1.59
FR1	15.27	1.14
FR1	10.31	1.00
FR1	6.11	0.53
FR1	5.50	0.89
FR1	5.38	0.51
FR1	3.96	0.69
FR1	4.53	0.67
FR1	3.84	0.43
FR2	3.86	0.38
FR3	2.78	0.34
FR3	2.91	0.39
FR3	2.67	0.35
FR5	1.94	0.32
FR5	2.18	0.28
FR5	2.10	0.34
FR5	1.67	0.25
FR8	1.18	0.13
FR8	1.76	0.26
FR8	1.42	0.17
FR8	1.51	0.18

Table 1c

XX0.5 self-administration

Active nose-pokes (Mean ± SEM)

(n=9)

Fixed Ratio	Mean	SEM
FR1	57.99	6.90
FR1	26.14	4.32
FR1	14.93	2.40
FR1	14.73	3.92
FR1	14.18	2.80
FR1	7.08	1.48
FR1	3.79	1.03
FR1	4.65	0.93
FR1	4.28	1.24
FR2	5.12	1.09
FR3	4.81	1.44
FR3	3.75	0.61
FR3	3.86	1.11
FR5	4.17	1.18
FR5	4.78	1.26
FR5	3.48	0.80
FR5	2.87	0.78
FR8	3.06	0.85
FR8	8.83	1.60
FR8	2.97	0.83
FR8	5.95	1.02

Table 2c

XX0.5 self-administration

Inactive nose-pokes (Mean ± SEM)

(n=9)

Fixed Ratio	Mean	SEM
FR1	31.14	4.93
FR1	21.44	4.47
FR1	11.94	3.39
FR1	12.36	3.92
FR1	12.18	2.95
FR1	5.63	1.32
FR1	4.66	1.26
FR1	4.36	1.09
FR1	4.71	1.06
FR2	3.88	0.99
FR3	4.06	0.59
FR3	4.56	0.80
FR3	2.36	0.55
FR5	4.56	1.34
FR5	7.46	2.48
FR5	4.15	1.43
FR5	3.06	0.97
FR8	3.02	0.86
FR8	6.48	1.64
FR8	5.43	1.21
FR8	6.81	1.59

Table 3c

XX0.5 self-administration

Infusions (Mean ± SEM)

(n=9)

Fixed Ratio	Mean	SEM
FR1	19.48	1.60
FR1	14.09	1.53
FR1	8.46	1.25
FR1	7.05	1.03
FR1	5.83	1.03
FR1	4.42	0.65
FR1	2.77	0.60
FR1	3.09	0.39
FR1	2.46	0.42
FR2	2.12	0.23
FR3	1.85	0.31
FR3	1.47	0.17
FR3	1.63	0.27
FR5	1.59	0.24
FR5	1.38	0.21
FR5	1.26	0.14
FR5	1.32	0.18
FR8	1.17	0.11
FR8	1.61	0.24
FR8	1.17	0.11
FR8	1.17	0.11

Table 1d

XX1 self-administration

Active nose-pokes (Mean ± SEM)

(n=10)

Fixed Ratio	Mean	SEM
FR1	34.79	6.51
FR1	31.84	7.01
FR1	18.68	6.16
FR1	15.59	4.28
FR1	13.02	4.46
FR1	13.14	4.41
FR1	8.69	2.77
FR1	7.20	2.52
FR1	5.99	1.85
FR2	8.09	2.23
FR3	7.35	2.33
FR3	6.22	1.82
FR3	3.01	0.73
FR5	6.09	1.24
FR5	7.39	2.08
FR5	6.75	1.70
FR5	8.54	1.46
FR8	6.76	1.58
FR8	7.06	2.28
FR8	5.13	1.48
FR8	6.75	1.42

Table 2d

XX1 self-administration

Inactive nose-pokes (Mean ± SEM)

(n=10)

Fixed Ratio	Mean	SEM
FR1	22.68	3.40
FR1	22.13	4.64
FR1	15.99	4.42
FR1	14.06	4.13
FR1	12.23	3.38
FR1	7.19	2.42
FR1	8.49	2.71
FR1	7.60	2.50
FR1	4.45	1.17
FR2	7.22	2.29
FR3	6.63	1.77
FR3	7.16	1.81
FR3	4.83	1.22
FR5	6.34	2.01
FR5	10.05	2.08
FR5	6.41	1.21
FR5	5.76	1.50
FR8	5.36	1.57
FR8	7.06	1.44
FR8	5.78	1.88
FR8	8.32	1.81

Table 3d

XX1 self-administration

Infusions (Mean ± SEM)

(n=10)

Fixed Ratio	Mean	SEM
FR1	16.00	2.14
FR1	16.11	2.63
FR1	9.30	1.97
FR1	8.08	1.56
FR1	7.46	1.65
FR1	6.14	1.36
FR1	4.24	1.01
FR1	3.70	0.88
FR1	3.51	0.73
FR2	3.36	0.57
FR3	2.21	0.53
FR3	2.41	0.46
FR3	1.53	0.21
FR5	1.55	0.24
FR5	1.71	0.29
FR5	1.79	0.32
FR5	1.83	0.25
FR8	1.43	0.20
FR8	1.64	0.29
FR8	1.32	0.19
FR8	1.37	0.17

Table 4a

Effect of XX on cocaine self-administration

Active nose-pokes (Mean ± SEM)

(n=7)

Treatment	pre	SEM	post	SEM
0	184.79	42.22	189.85	40.86
10	158.91	28.58	149.69	29.49
30	165.36	33.17	160.23	34.62
100	190.49	47.35	35.71	17.91

Table 4b

Inactive nose-pokes (Mean ± SEM)

(n=7)

Treatment	pre	SEM	post	SEM
0	25.92	7.61	25.08	8.69
10	19.99	7.34	17.39	5.15
30	17.66	9.16	17.50	9.72
100	28.08	13.94	12.47	6.44

Table 5

Self-Infusions (Mean ± SEM)

(n=7)

Treatment	pre	SEM	post	SEM
0	15.27	1.88	16.54	2.03
10	15.08	1.81	14.72	1.81
30	15.10	2.07	13.63	1.72
100	14.81	2.12	4.73	1.35

Table 6

Effect of XX on cocaine self-administration

Locomotor activity

(Mean ± SEM)

(n=7)

Treatment	pre	SEM	post	SEM
0	539.05	152.37	483.68	150.43
10	523.85	185.13	391.55	156.67
30	531.75	198.89	286.43	126.40
100	594.14	181.09	195.76	81.32

Table 7a

Effect of XX60 on cocaine self-administration

Active nose-pokes (Mean ± SEM)

(n=5)

Treatment	pre	SEM	post	SEM
0	305.13	44.84	281.96	59.37
60	253.88	48.73	174.62	34.44

Table 7b

Effect of XX60 on cocaine self-administration

Inactive nose-pokes (Mean ± SEM)

(n=5)

Treatment	pre	SEM	post	SEM
0	14.24	6.38	24.07	6.92
60	16.00	5.86	13.12	3.45

Table 8

Effect of XX60 on cocaine self-administration

Self-infusions (Mean ± SEM)

(n=5)

Treatment	injb	SEM	injt	SEM
0	18.03	2.38	18.48	2.60
60	18.72	2.27	11.83	1.63

Table 9

Effect of XX60 on cocaine self-administration

Locomotor activity (Mean ± SEM)

(n=5)

Treatment	pre	SEM	post	SEM
0	529.74	144.23	549.97	164.68
60	451.74	122.35	220.59	50.81

Table 10

Effect of amphetamine on cocaine self-administration

Active and inactive nose-pokes and Infusions (Mean ± SEM)

(n=6)

Treatment	active hole	SEM	inactive hole	SEM	infusions	SEM
vehicle	240.62	55.12	9.61	1.87	17.84	2.83
amphetamine (2,5 mg/kg)	81.25	48.41	19.68	9.47	8.15	2.85

Table 11

Effect of amphetamine on cocaine self-administration

Locomotor activity (Mean ± ESM)

(n=6)

Treatment	locomotor activity	ESM
vehicle	513.12	131.02
amphetamine (2,5 mg/kg)	591.63	132.25

Table 12

Body weight

Grams (Mean ± SEM)

	20/12/2001		04/01/2002		11/01/2002		22/01/2002		29/01/2002		05/02/2002		08/02/2002		13/02/2002		20/02/2002	
group	**bw**	**SEM**	**bw**	**SEM**	**bw**	**SEM**	**bw**	**SEM**	**bw**	**SEM**	**bw**	**SEM**	**bw**	**SEM**	**bw**	**SEM**	**bw**	**ESM**
coc	310	2.78	387	3.53	407	4.35	440	6.23	427	6.88	424	10.70	433	9.36	444	13.34	450	17.28
xx0.25	316	2.36	392	3.44	415	4.81	445	5.89	443	6.79	446	6.69	448	6.32	460	7.33	463	11.35
xx0.5	317	2.12	392	4.58	419	5.68	449	6.58	456	4.83	459	5.84	458	5.35	464	8.23	467	7.53
xx1	318	2.25	394	5.05	415	5.55	445	6.90	442	6.10	449	6.63	449	7.93	456	13.26	472	9.67