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EFFECTS OF THREE STIMULANT DRUGS ON AUTOSHAPING AND POSITIVE AUTOMAINTENANCE BASELINES WITH RATS.

LOS EFECTOS DE TRES DROGAS ESTIMULANTES SOBRE LINEAS BASES DE AUTOMOLDEAMIENTO Y AUTOMANTENIMIENTO POSITIVO CON RATAS

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RESUMEN

Los efectos de tres drogas estimulantes, cocaína, cafeína y picrotoxina, se evaluaron usando ratas como sujetos, se emplearmn procedimientos de automoldeamiento modificado, operante y automantenimiento positivo, clásico como líneas de base. Las diferentes dosis de droga, espaciadas logarítmicamente, se inyectaron intraperitonealmente. El procedimiento de automoldeamiento modificado, operante, fue insensible a todas excepto una de las diferentes dosis de droga empleadas. El procedimiento de automantenimiento positivo, clásico, fue afectado diferencialmente por las drogas: en el grupo de cocaína, se obtuvo una función U invertida; en el grupo de cafeína se obtuvo una función decreciente y en el grupo de picrotoxina se obtuvo una función U invertida. Se discute el uso de los procedimientos en farmacología conductual.

Palabras Clave: Automantenimiento Positivo, Automoldeamiento, Cafeína, Cocaína, Drogas Presión de Palanca, Picrotoxina, Ratas.

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ABSTRACT

The behavioral effects of three stimulant drugs, cocaine hydrochloride, caffeine, and picrotoxin were evaluated on rats using a modified autoshaping, operant, and a positive automaintenance, classical, baseline procedure. Different doses of the drugs, logarithmically spaced, were injected intraperitoneally. The modified autoshaping, operant procedure was insensitive to all but one of the different doses of the drugs used. The positive automaintenance, classical procedure was differentially affected by drugs: in the cocaine group, an inverted U function was observed; in the caffeine group, a decreasing function; and in the picrotoxin group, an inverted U function was obtained. The use of the procedures in behavioral pharmacology is discussed.

Key Words: Autoshaping, Caffeine, Cocaine, Drugs, Lever Press, Picrotoxin, Positive Automaintenance, Rats.

The autoshaping paradigm (Brown & Jenkins, 1968) using rats as subjects (Atnip, 1977) has been used to evaluate the effects of different experimental manipulations on positively reinforced behaviors. Bermúdez-Rattoni, Mujica-Gonzalez, and Prado-Alcalá (1986), studied the effect of scopolamine injections (30 μg/3 μl) in the caudate putamen of rats. Using an autoshaping procedure they found a retardation on the acquisition of leverpressing responding. Cohen, Messing, and Sparber (1987), studied the effects of trimethyltin (TMT, a organometal neurotoxin) on an autoshaping procedure with a delay of reinforcement. Under a constant 6 s delay , doses of 3.0 and 6.0 TMT mg /kg produced a graded reduction in responses to the lever. However, a dose of 7.5 TMTmg/kg did not produce as great an effect as the lower doses. Díaz Del Guante, Carbonell-Hernandez, Quirarte, Cruz-Morales, Rivas Arancibia, and Prado-Alcalá (1993), found that choline injections (9 μg/3 μl), in the striatum of rats, produced a marked facilitation on the acquisition of conditioned responses in a classical-operant, in which both types of contingencies classical and operant were present and an operant autoshaping procedure in which a response was necessary for the delivery of the reinforcer. Minkin, Meyer, and van Haaren (1993), used an autoshaping procedure to evaluate the effects of chronic administration of an anabolic steroid (nandrolone decanoate, in intramuscular injections of 0.0, 10.0, 50.0 mg/0.2 ml), had on learning the lever press response. They found no effects of the steroid on learning in this procedure. In another example of the use of the autoshaping procedure, Mundy and Iwamoto (1987) used this procedure, with rats as subjects, as a learning/memory model, to study the effects of desglycinamide arginine vasopressin (DGAVP), a vasopressin analog, in10.0 to 30.0 μg/kg subcutaneously administered doses and scopolamine (SCOP) in 0.1 to 0.8 mg/kg intraperitoneally administered doses. In this experiment, DGVAP had no effect on autoshaped lever touch responses; SCOP impaired acquisition of the autoshaped lever touch response, but did not alter responding in animals that already had the lever touch response. In another

experiment, Mundy and Iwamoto (1988), found that a 0.45 mg/kg subcutaneously administered dose of nicotine, either immediately or 5 min after each session, impaired the autoshaping of the lever-touch response. Oscos, Martinez and McGaugh (1988) also using autoshaping found that rats receiving an intraperitoneally administered, 1.0 mg/kg dose of d-amphetamine, immediately after the first training session, made significantly more lever press responses during the presentation of the conditioned stimulus than rats receiving either 2.0 mg/kg of the same drug, or 1.0 mg/kg two hours before each conditioning session. Poling and Thompson (1977), found that under a positive automaintenance procedure in which food was delivered after the key light was turned off, with pigeons as subjects, intramuscularly administered doses of 0.5, 1.0, and 2.0 mg/kg of amphetamine, produced a dose-dependent and rate independent decrement in keypecking. Steckler, Andrews, Marten, and Turner (1993), found that ibotenic acid (0.06 M) infused into the basal forebrain of rats, increased the number of trials to reach a learning criterion that required five consecutive lever presses in an autoshaping procedure. In groups either infused with quisqualic acid (0.12 M) or sham operated, the effect was not as large, compared with groups in which ibotenic acid was infused.

As the preceding studies show, the autoshaping procedure in its different forms has been used as a procedure in which classical or operant contingencies may be programmed to study the effects of different drugs. On the autoshaping procedure there are two types of contingencies. During the first stage of acquisition a classical conditioning contingency operates until the first peck or leverpress emerges. Afterwards, an operant contingency is introduced. If only the classical contingency is in effect, the resulting procedure is called positive automaintenance or *classical*. If on the contrary, a response is required to present the unconditioned stimulus, the procedure that results has been called *operant* (Atnip, 1977). Atnip (1977) has shown that in these "autoshaping" procedures, classical and operant, the leverpressing response is acquired to the same terminal level. Atnip (1977) also mentions that: "The operant and classical procedures did not differ in overall terms, but in individual-subject terms, the operant procedure might be considered superior, in that it yielded acquisition in all six subjects, *versus* acquisition in only four of six subjects in the classical procedure." (p. 66). In behavioral pharmacology (Weiss & Laties, 1975) different drugs have been administered on known behavioral processes to screen the effects of the substances. Spealman, Katz, and Witkin (1978) found that pentobarbital in doses from 1.0 to 17.0 mg/kg had different effects on keypecking in a two key, stimulus key and operant key, multiple variable-interval extinction (*mult* VI EXT) schedule; pentobarbital selectively increased the rate of responding on the stimulus key, while the same doses had little effect or decreased keypecking on the operant key. Spealman et al. also found that d-amphetamine, in doses from 0.1 to 5.6 mg/kg decreased or had little effect on keypecking on both keys. In the present paper, the operant and classical procedures were used to evaluate the effects of three stimulant drugs, caffeine, cocaine and picrotoxin to determine the generality of the results obtained by Spealman et al. (1978) with d-amphetamine. Although the stimulant drugs used in this experiment have different

neurochemical mechanisms of action, cocaine and caffeine act on dopamine and picrotoxin on GABA, it was not expected to discriminate between them with the procedures used in this study. The operant procedure (Atnip, 1977), in which a leverpress is required to produce immediate water reinforcement, was used as an example of an operant contingency. The classical procedure in which the unconditional stimulus (US) water, is presented at the end of the 8 s conditional stimulus (CS), lever insertion, was used as an example of a classical contingency. These procedures were used in different groups, because the possibility of adventitious reinforcement that may exist in the two key multiple schedule, as in the Spealman et al. study, is avoided. It was the aim of this study to find if the two experimental procedures that were used could produce different patterns of responding for the three stimulants, on behavior maintained by operant or classical contingencies. It is expected that use of these procedures may represent a technique to study new drugs preclinically, before they are administered to humans, and possibly detect which type of behavior, operant or respondent, those new drugs will affect.

METHOD

Subjects

Twenty four male Wistar strain rats were used. They were experimentally naive and under a 23.5 hour water deprivation regime. The animals were 120 days old when the experiment started.

Drugs

Drugs were injected intraperitoneally in a 2.0 ml/kg volume, dissolved in isotonic saline. Cocaine hydrochloride (SSA), caffeine (Sigma), and picrotoxin (Sigma) were used. The weight depicted on tables refers to the compound.

Apparatus

A Coulbourn rodent operant conditioning chamber Model E10-10, was used. It had a BRS/LVE (RRL-015) retractable lever that, on insertion, initiated trials. Water reinforcement was delivered by a solenoid activated 0.01 cc dipper. A Commodore 64 computer coupled to an interface built ad hoc was used to deliver experimental events and to record data. Masking noise was always present in the experimental chamber.

Procedure

On a first session a variable time (VT) schedule delivered 50 response independent reinforcers to each rat. Afterwards the rats were randomly assigned to six different groups. Half of the subjects were run in an operant procedure in which a response was required for the presentation of the US, and the other half in a classical procedure in which no response was required for the presentation of the US, until 500 trials were completed in 20 sessions of 25 trials each one. A trial consisted on the insertion of the right lever as CS, into the experimental chamber. The trials, 8 s long, were scheduled by a variable time VT 80 s schedule of reinforcement using

the progression of Fleshler and Hoffman (1962). Each leverpress was counted as response. The conditions of the experimental groups, the drugs, and the doses are presented on Table I.

TABLE I

Shows the Groups, Drugs, and Doses

Cocaine hydrochloride	Doses					
Group Autoshaping (N=4)	0.0625	0.125	0.25	0.5	1.0	2.0
Group Automaintenance (N=4)	0.0625	0.125	0.25	0.5	1.0	2.0

Caffeine	Doses				
Group Autoshaping (N=4)	5.0	10.0	20.0	40.0	80.0
Group Automaintenance(N=4)	5.0	10.0	20.0	40.0	80.0

Picrotoxin	Doses				
Group Autoshaping (N=4)	0.185	0.375	0.75	1.5	3.0
Group Automaintenance (N=4)	0.185	0.375	0.75	1.5	3.0

After 500 trials had been completed in 20 sessions of 25 trials each one, the animals were injected ip with isotonic saline (NaCl) on session 21 and every other day they received a different dose of the drug on a random sequence. On no-drug days, 25 trials of the operant or the classical procedure, were run, depending on the group to which rats were assigned.

RESULTS

Figure 1 shows the mean percentage of trials with a response for the cocaine hydrochloride groups (N = 4 per group), for the last five baseline sessions, the NaCl session, and the five drug sessions. The pattern of responding in the classical group is a decreasing function of dose. A quadratic function has been fitted to the data to give a quantitative description of the percentage of responding at the different drug doses and is presented in the Appendix. The percentage of trials with a response in the operant group did not show any effect at any dose.

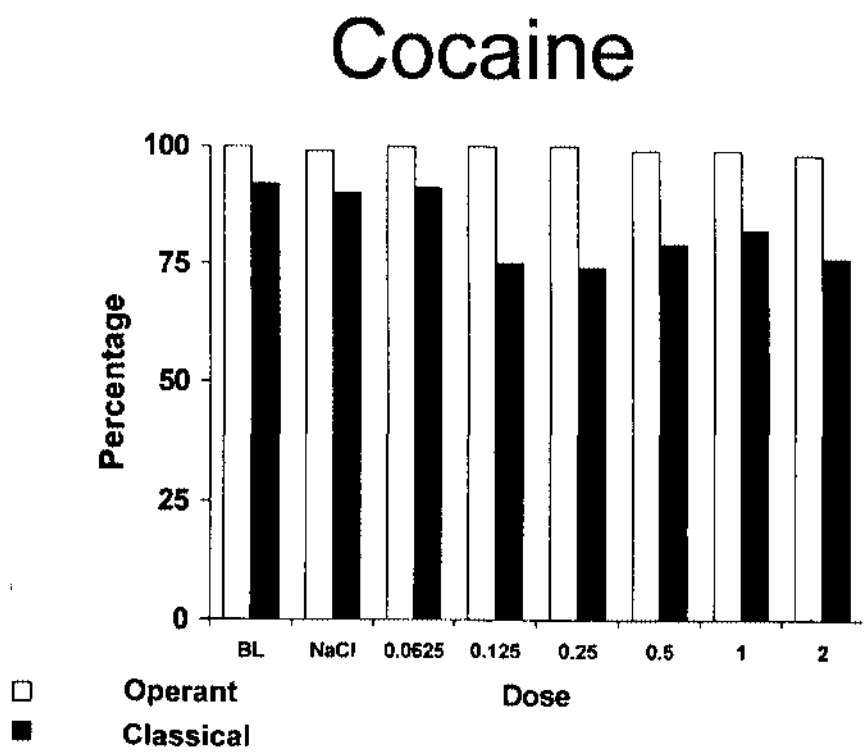

Figure 1. Percentage of trials with a response for the cocaine group. The empty bars represent the operant procedure, the filled bars represent the classical group. Bars represent means of four subjects.

Figure 2 shows the mean percentage of trials with a lever pressing response for the caffeine groups (N = 4 per group), for the last five baseline sessions, the NaCl session, and the six drug sessions. The classical group shows a decreasing percentage of trials with a response as the dose increases. A quadratic function has been fitted to the data to give a quantitative description of the percentage of responding at the different drug doses and is presented in the Appendix. In the operant group, increasing doses of the drug produced no effects.

Figure 3 shows the mean percentage of trials with a response from the picrotoxin groups (N = 4 per group), for the last five baseline sessions, the NaCl session, and the five drug sessions. The percentage of trials with a response from the classical group has an inverted U-shaped function, beyond the first dose. A quadratic function has been fitted to the data to give a quantitative description of the percentage of responding at the different drug doses and is presented in the Appendix. Subjects in the operant group were affected only by the fourth and fifth doses. Both groups of subjects stopped responding with the largest dose.

In summary, the classical groups were affected by the different drug doses in the percentage of trials with a response measure. The operant groups did not show any effect in the trials with a response data.

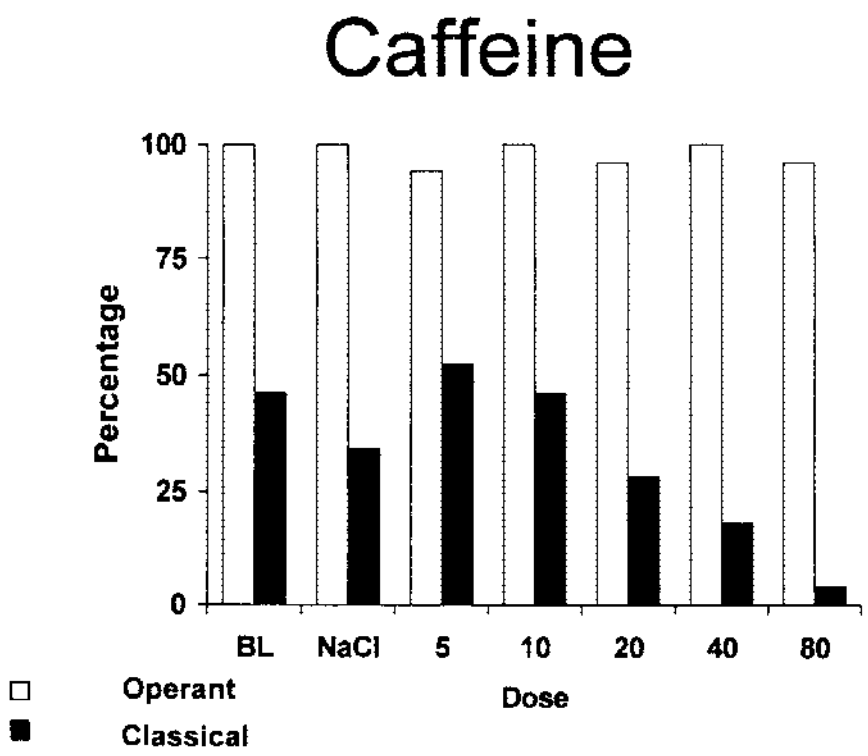

Figura 2. Percentage of trials with a response for the caffeine group. The empty bars represent the operant procedure, the filled bars represent the classical group. Bars represent means of four subjects

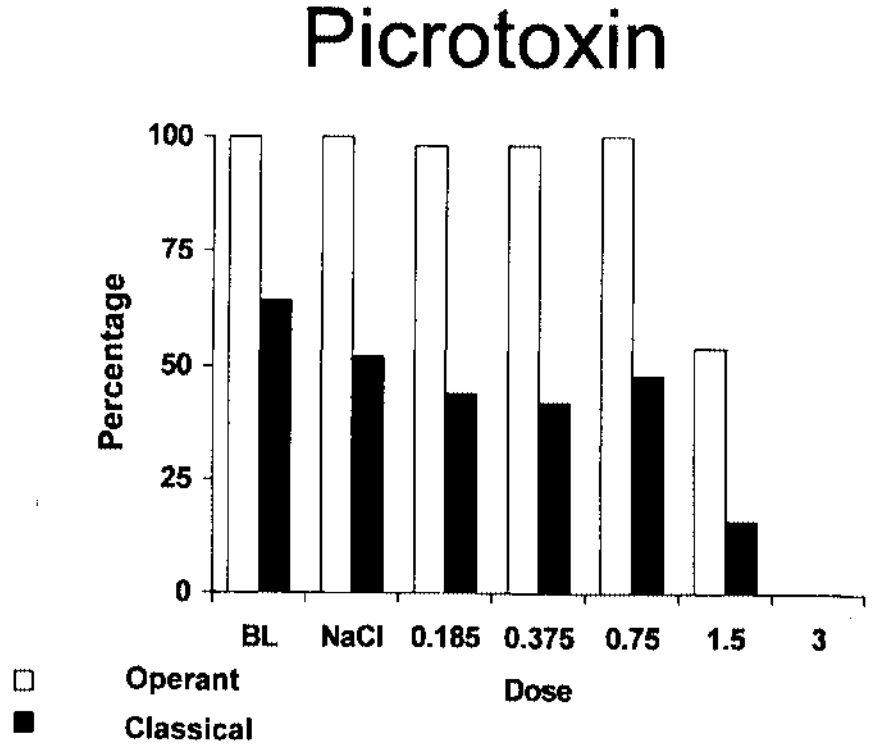

Figure 3. Percentage of trials with a response for the picrotoxin group. The empty bars represent the operant procedure, the filled bars represent the classical group.Bars represent means of four subjects.

DISCUSSION

This experiment compared the effects of three stimulant drugs, cocaine hydrochloride, caffeine, and picrotoxin on two procedures, operant and classical, each representing instrumental and Pavlovian paradigms, respectively, as Atnip (1977) has shown. Only the classical groups showed an effect of the different doses of the drugs. The main effect was a inverted U function in the cocaine hydrochloride group; a decreasing function in the caffeine group; and an inverted U function in the picrotoxin group.The operant groups were insensitive to the different doses of drugs, except for the largest dose of picrotoxin. This aspect of the data shows that

responding produced by the operant procedure makes the responses resistant to the particular doses and drugs used in this experiment. The results of this experiment are consistent with those obtained in the Spealman et al. (1978) work. In that study different doses of d-amphetamine produced a greater decrease in key pecking responding to the stimulus, classical key, than to the constant, operant key. The number of responses were higher for the constant, or operant key, than for the stimulus, or classical key. In the present study different doses of stimulant drugs produced little change in leverpressing responding in the operant procedure or a decrease in leverpressing responding in the classical procedure. The percentage of trials with a response was higher in the operant groups than in the classical groups. It may be added that in the present experiment the use of different groups to evaluate responses maintained by different contingencies avoided adventitious reinforcement, as in the Spealman et al. two key procedure.

As Colotla, Gutierrez, Ramos, and Arriaga (Note 1) mentioned, the effects of drugs over these stimulus-reinforcer contingency procedures deserves a thorough study. The operant procedure should be studied with care, because of its insensitivity to the range and progression of doses used in this particular experiment. One difference with the Spealman et al. (1978) study is that they used a geométric progression that tripled the preceding dose; in this study the progression only doubled the preceding dose. Maybe that increase in drug dosage produces greater effects than the present one.

Different studies have shown that the operant and the classical procedures are useful as *positively motivated baselines* for different manipulations (cf. Bermudez-Rattoni et al., 1986; Cohen et al., 1987; Díaz del Guante et al., 1993; Minkin et al., 1993; Mundy & Iwamoto, 1987; 1988; Oscos et al., 1988; Poling & Thompson, 1977; Steckler et al., 1993). However, the real usefulness of the procedures to study acquisition, learning, memory, or the effects of drugs on responses maintained by different contingencies remains to be investigated yet.

One finding that was unexpected was the effect seen with picrotoxin on the classical group. Franz (1981) affirms that "No effect of picrotoxin can be appreciated until convulsive doses are administered." (p. 582). In the present study, a intermediate effect was obtained with the fourth dose of picrotoxin in both procedures before the animals stopped responding at all with the largest one.

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APPENDIX

Quadratic fit and equation data from the three automaintenance groups of the experiment. Figures A1, A2, and A3 represent the functions fitted to the cocaine hydrochloride, caffeine, and picrotoxin groups, respectively. In each figure the legend presents the parameter values and the correlation coefficient

The $\underline{t}$ value for the non-linear correlation coefficient between percentage of trials with a response and the estimated function for the cocaine hydrochloride group, $\underline{t}=0.12$, $\underline{p}>0.05$, was not significant. The $\underline{t}$ value revealed a significant non-linear correlation for the caffeine and picrotoxin groups.. For the caffeine group $\underline{t}=8.53$, $\underline{p}<0.01$. For the picrotoxin group $\underline{t}=3.381$, $\underline{p}<0.05$.

Table II shows the numerical data, percentages,of trials with reponse, from the six groups.

Figure A1

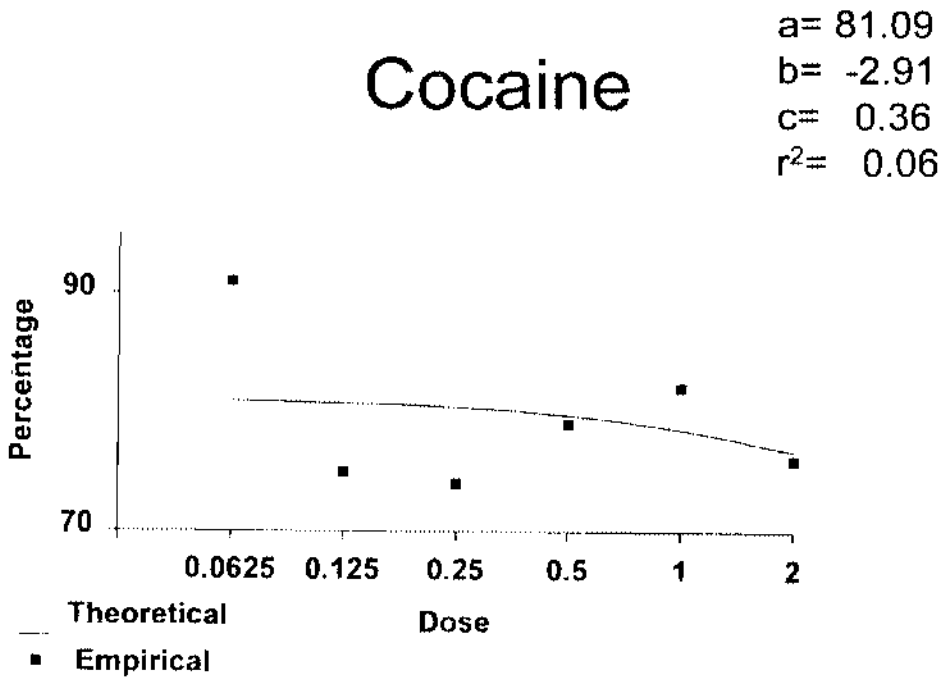

Figure A2

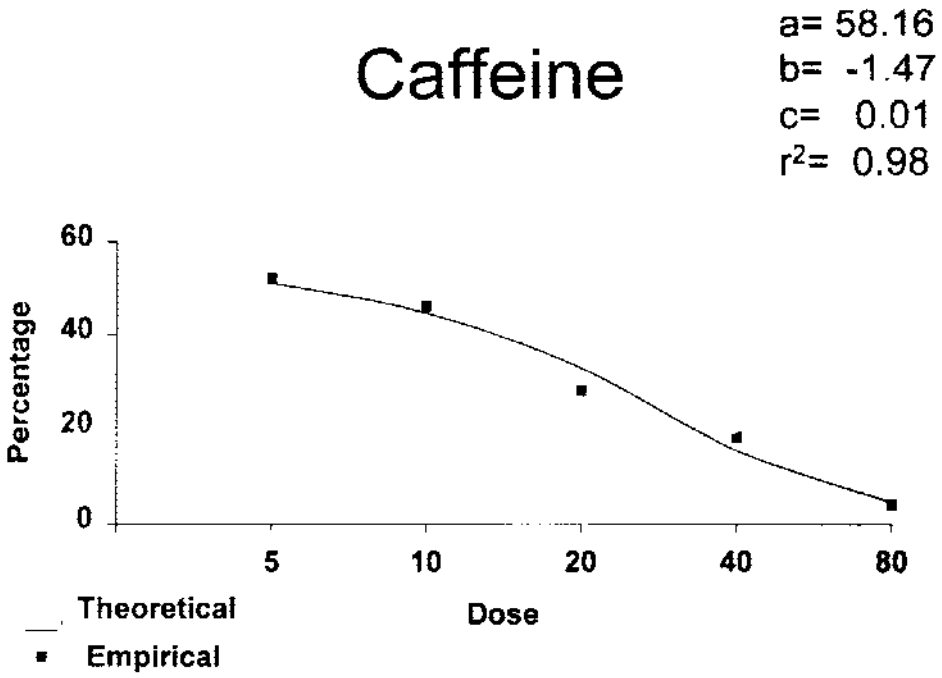

Figure A3

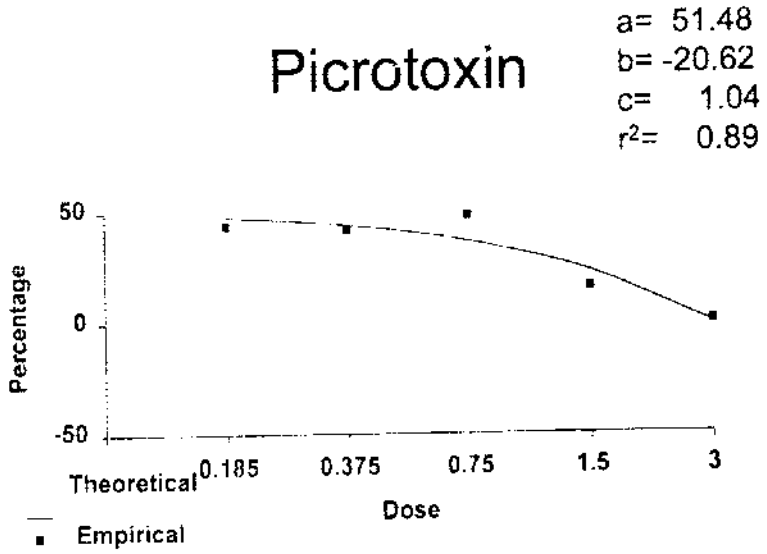

Table II

Shows the numerical data-pecentaje of trials with a reponse, from the six groups

Cocaine hydrochloride		
Procedure		
Dose	Autoshaping	Automaintenance
Base Line	100	92
Na Cl	99	90
0.0625	100	91
0.125	100	75
0.25	100	74
0.5	99	79
1.0	99	82
2.0	98	76

Caffeine		
Procedure		
Dose	Autoshaping	Automaintenance
Base Line	100	46
Na Cl	100	34
5.0	94	52
10.0	100	46
20.0	96	28
40.0	100	18
80.0	96	4

Picrotoxin		
Procedure		
Dose	Autoshaping	Automaintenance
Base Line	100	64
Na Cl	100	52
0.185	98	44
0.375	98	42
0.75	100	48
1.5	54	16
3.0	0	0