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Anticipatory conditioned responses to subjective and physiological effects of heroin in addicted persons

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ABSTRACT. *Study 1:* The aim of this experiment was to analyze in persons detoxified of heroin, conditioned responses (CRs) that are opposite to the unconditioned physiological and subjective effects that are induced by this substance. The basic procedure consisted in presenting slides with images of neutral stimuli (NSs) and conditioned stimuli (CSs) of heroin to both non-addicted and detoxified addicted persons. The evaluated responses were conductance (C) and self-perception of abstinence symptoms (SAS). The results are considered to be indicators of compensatory conditioned responses (CCRs) (conditioned abstinence). *Study 2:* The aim of this experiment was to facilitate the emission of mimetic conditioned responses (MCRs) to the unconditioned subjective effects of heroin in detoxified heroin addicts. Three different stimulus series were manipulated: SA, during which the participant remained alone; SB, administration of a needle prick given by the researcher; SC, performance of the «pump» ritual without drug by the participants. The response measured was SAS. The results are considered to be indicators of MCRs. The results of both studies are discussed in the context of the environmental specificity model of anticipatory responses to the effects of drugs.

KEY WORDS. Heroin dependence. Conditioned abstinence. Mimetic responses. Experiment.

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RESUMEN. *Estudio 1:* El objetivo de este experimento fue analizar en personas desintoxicadas a la heroína respuestas condicionadas (RCs) opuestas a ciertos efectos fisiológicos y subjetivos de esta droga. El procedimiento consistió en presentar diapositivas con imágenes de estímulos neutros (ENs) y estímulos condicionados (ECs) de la heroína a personas no adictas y a personas adictas desintoxicadas. Las respuestas evaluadas fueron conductancia (C) y autopercepción de síntomas de abstinencia (ASA). Los resultados se consideraron como indicadores de respuestas condicionadas compensatorias de los efectos de la heroína (abstinencia condicionada). *Estudio 2:* El objetivo de este experimento fue facilitar en personas adictas desintoxicadas a la heroína la emisión de respuestas condicionadas miméticas (RCMs) de los efectos subjetivos incondicionados de la heroína. Para ello se utilizaron tres series estimulares: SA, serie control; SB, el investigador administra un leve pinchazo; SC, el participante realiza el ritual de "bombeo" sin droga. La respuesta medida fue ASA. Los datos obtenidos se consideraron como indicadores de RCMs. Los resultados de ambos estudios se discutieron desde el modelo de la especificidad ambiental de las respuestas anticipatorias de los efectos de las drogas.

PALABRAS CLAVE. Dependencia a la heroína. Abstinencia condicionada. Respuestas miméticas. Experimento.

RESUMO. *Estudo 1:* O objectivo desta experiência foi analisar em pessoas desintoxicadas de heroína, respostas condicionadas que são opostas a certos efeitos incondicionados fisiológicos e subjectivos desta droga. O procedimento consistiu em apresentar diapositivos com imagens de estímulos neutros (ENs) e estímulos condicionados (ECs) da heroína a pessoas não aditas e a pessoas aditas desintoxicadas. As respostas avaliadas foram condutância (C) e autopercepção de sintomas de abstinência (ASA). Os resultados consideraram-se como indicadores de respostas condicionadas compensatórias dos efeitos da heroína (abstinência condicionada). *Estudo 2:* O objectivo desta experiência foi facilitar em pessoas aditas desintoxicadas da heroína a emissão de respostas condicionadas miméticas (RCMs) dos efeitos subjectivos incondicionados da heroína. Para isso utilizaram-se três séries de estímulos: SA, série controlo; SB, o investigador administra uma leve picada; SC, o participante realiza o ritual de "bombear" sem droga. A resposta medida foi ASA. Os dados obtidos consideraram-se como indicadores de RCMs. Os resultados de ambos os estudos são discutidos a partir do modelo da especificidade ambiental das respostas antecipatórias dos efeitos das drogas.

PALAVRAS CHAVE. Dependência da heroína. Abstinência condicionada. Respostas miméticas. Experiência.

Introduction

According to the literature, the effects of drugs can be altered in certain ways by non-pharmacological factors (Arnold, Robinson, Spear, and Snotherman, 1993; Childress, Hole, Ehrman, Robbins, McLelland, and O'Brien, 1993; Cole, Sumnall, O'Shea, and Marsden, 2003; Hinson and Siegel, 1983; King, Joyner, and Ellinwood, 1994; Krank,

1987; Pavlov, 1927; Schwart-Stevens and Cunningham, 1993; Sell, Morris, Bearn, Frackowiak, Friston, and Dolan, 2000; Thompson and Ostlund, 1965; Tzschentke, 2004; Wikler, 1948, 1973a, 1973b; Zheng, Tan, Luo, Xu, Yang, and Sui, 2004). This means that the result of the chemical stimulation occasioned by different drugs may depend not only on pharmacokinetic and pharmacodynamic factors but also on the experience of using these substances in specific contexts, where Pavlovian conditioning factors may be in effect. Along general lines, behavioral theories about the intensity and direction of responses to stimuli associated with the effects of opiates basically propose two global hypotheses regarding the effects of these stimuli on the response systems of organisms biologically detoxified of these drugs. One hypothesis, compensatory conditioned responses (CCRs) hypothesis, states that certain stimuli associated with the effects of withdrawal and with the biological responses of homeostatic regulation of the neurochemical action of heroin compounds could come to evoke conditioned responses of tolerance and/or abstinence (Bespalav, Zvartau, and Beardsley, 2001; Childress, McLelland, Natale, and O'Brien, 1987; Childress, McLelland, and O'Brien, 1986; Ehrman, Ternes, O'Brien, and McLelland, 1992; Falls and Kelsey, 1989; Foo, 1999; Grabowski and O'Brien, 1981; Hinson and Siegel, 1983; Litteton and Little, 1989; Ternes and O´Brien, 1990; Tiffany, Maude-Griffin, and Drobes 1991; Trujillo, 1997; Wikler, 1973a,1973b, 1980). Occasionally, certain conditioned stimuli (CSs) belonging to the habitual context of the addict could evoke CRs opposite to the effects of the heroin, and, if the substance is administered could compensate for them. On the other hand, if the drug is not given in the presence of these stimuli, the CRs could be perceived as abstinence symptoms (conditioned abstinence). This may mean that the CRs of tolerance and abstinence are two manifestations of the same phenomenon, with these possibly being under the control of the same mechanisms of conditioning (Litteton and Little, 1989; Trujillo, 1997). This means that the phenomenon of the environmental specificity of tolerance observed in the presence of certain CSs when heroin is administered should have a high level of covariation with the appearance of CCRs in the presence of these same stimuli when the drug is not administered. Although there have been various studies done in this area, the obtained results are not all consistent with what one would expect within the planned conceptual scheme (Baker and Tiffany, 1985; Eikelboom and Stewart, 1982; Paleta and Wagner, 1986; Robbins and Eherman, 1991). However, even though data from various studies have indicated the existence of the environmental specificity of opiate tolerance (Litteton and Little, 1989; Siegel, 1988; Tiffany, Petrie, Martin, and Baker, 1983), at times there has been no demonstration of the compensatory CRs that are hypothesized to modulate this tolerance. As such, the non-detection of these responses has resulted in the idea at certain scientific levels that the model of conditioned abstinence remains a «moot question» (Goudie and Griffiths, 1986). The second hypothesis, mimetic conditioned responses (MCRs) hypothesis, states that these conditioned stimuli (CSs) of the drug might elicit conditioned responses (CRs) similar to the unconditioned effects that these opiates induce (Hinson and Poulos, 1981; Kalinichev, White, and Holtzman, 2004; Lett, 1989; Levine, 1974; Stockhorst, Steingrüber, and Scherbaum, 2000; Trujillo, 1997; Xigeng *et al*., 2004). According to the literature, not all the anticipatory CRs evoked by the CSs of heroin are opposite to

the effects of heroin. In other words, some of these responses appear to imitate more than compensate the drug's effects. As occurs with the CCRs, in the appearance of the MCRs to the unconditioned effects of heroin, the same associative mechanisms might be involved. In this case, the association could occur between environmental stimuli present at the moment of drug administration and the direct unconditioned effects that the drug induces, where the CRs would imitate such effects and would make them stronger when the drug is administered under the control of the specific conditioned environment (conditioned sensitivity). This means anticipatory responses with conditioned sensitivity and conditioned tolerance respectively, also known as mimetic and compensatory CRs to the unconditioned effects of the opiates (Childress *et al.,* 1987; Hinson and Siegel, 1982; Philips, Goosop, and Bradley, 1986; Rochford and Stewart, 1987; Trujillo, 1997).

In regard to the direction of the pharmacological CRs, frequently one observes the appearance of not only CRs those are compensatory but also mimetic to the unconditioned effects of the drug. Nevertheless, the conditions that favor the appearance of each of these two forms of response are still not clear. However, there are few studies done with humans that contribute data sufficiently consistent with the proposed model. In summary, it would seem that the mediating variables in these phenomena and the mechanisms by which they are organized are, at least in part, unknown.

The general structure of this experiment follows the procedures suggested by Ramos-Alvarez and Catena (2004), and the general methodology for classification and description proposed by Montero and León (2005).

STUDY 1

The aim of this study was to analyze, in persons organically detoxified of heroin, the magnitude and topography of conductance responses (C) and self-perception of abstinence symptoms (SAS) in the presence of contextual stimuli of heroin (CS) associated in the past with physiological and subjective states of abstinence, and at the same time with biological states consequent to processes of the organism's homeostatic regulation to the unconditioned effects of the opiate (Litteton and Little, 1989). In other words, the study's objective was to detect, after presentation of CSs, different compensatory-type CRs (CRs of abstinence) to the sedative and subjective effects that the substance induces. The present study ascribes to the model of environmental specificity of CCRs (tolerance or abstinence syndrome described).

Method

Participants

Two groups of voluntary persons participated in this study. The first group, termed the control group (CG), included 12 men and 12 women who had never had any direct experience with opiate drugs, but had sporadic contact with tobacco and alcohol. Their ages ranged from 25 to 32 years, with a mean (M) of 29.30 years, and standard deviation

(SD) of 2.11.The second group, the experimental group (EG), was also composed of 12 men and 12 women, with the same age range as the CG, a M of 28.80 years, and a SD of 2.30. All the EG participants had used tobacco, alcohol, cannabis, and psychoactive substances. Besides, they had direct experience with heroin (diacetylmorphine) through intravenous administration during a minimum of 58 months, and had reached a high level of addiction. The EG persons had been detoxified, for three months, from all the above-mentioned substances. They had sporadic contact with tobacco and alcohol. During the running of the study, they were in the drug dishabituation phase, without any medication.

Stimulus material

Eight different slides were used; four made of neutral stimuli (NSs) and four of conditioned stimuli (CSs). The NSs, termed NS1, NS2, NS3, and NS4, were composed of achromatic images of unfamiliar shapes. The CSs, termed CS1, CS2, CS3, and CS4, showed compound stimuli composed of images of acts and utensils related to the habitual preinjection setting of heroin, and as such, frequently associated with states of abstinence. The EG participants were asked, a week before, to order the four CS slides from least to most in their power to evoke desire for the drug. Ordering of stimuli by all 24 EG and CG participants were the same: CS1, CS2, CS3, and CS4. This arrangement likewise coincided with that predicted by the researchers, taking into account the number of stimulus elements that constituted each slide as a compound stimulus.

The sequential order of presentation of experimental conditions that constituted the stimulus series A, B, and C (SSA, SSB, SSC), each one presented in three consecutive daily sessions, was the following:

- SSA: (1) Five minutes of adaptation to the experimental chamber during which five flashes of white light in intervals of one minute were presented; (2) Presentation of the four NSs, each with a duration of three minutes, and a three minute darkened interval between each; and, (3) 40 seconds of darkness.
- SSB: The sequential order of this condition was the same as that used in SSA, the only difference being the substitution by CS4 for NS4.
- SSC: The sequential order of this condition was the same as that used in SSA, the only difference being that all four NSs were substituted by the 4 CSs.

Dependent variables

Two dependent variables were measured, under control of the above specified stimulus conditions. The physiological variable was electro-dermal activity (EA) and the subjective variable was SAS.

- Electrodermal activity (EA). This dependent variable was utilized due to its widespread use in research of the present study's kind, and to its being well know at the psycho-physiological level. It is known that the electrodermal response depends on the presecretory electrical activity of the sweat glands. To obtain these responses, a direct electrical current was applied externally. In this way, according to Ohm's law, one directly measures the electrical resistence of the

skin before the passage of the current. As a unit of measure of the EA, in terms of the skin's electrical resistence, the kilo-ohmnios was used. In other words, the intensity of the externally administered current was kept constant, and the voltage that passed through the organism was registered, this functioning as resistence. In this way, the obtained measurement was the skin resistence expressed in units of 1000 ohmnios. Finally, the values of resistence were transformed into values of conductance (C). The conductance in micro-mhos is equal to the reciprocal of the resistence in kilo-ohmnios multiplied by one thousand (Freixa i Baquè, 2001). As an index of the measure of EA, the amplitude of the response in conductance was used, which was considered a parameter of the specific electrodermal responses of the participants, in the presence of each of the stimuli that composed the stimulus series A, B, and C. Thus, the change in conductance, following transformation from the values of resistence, was analyzed from the start of the response to the point in which it reached its maximum level. In order to consider as specific the responses to each of the given stimuli, the following criteria were priory established: a) That the amplitude in change of response measured in electrical resistence of the skin be greater than 0.5 kilo-ohmnios; b) That the response start between 1 and 6s after the beginning of the stimulus presentation. However, for the application of this criterion, relatively lax, the modal response latency for each participant had previously been identified.

– Self-perception of abstinence symptoms (SAS). This was used as an index of abstinence. The self-perceived intensity of some corporal symptoms, similar to those that appear in the organic withdrawal syndrome of heroin, was measured. Participants were required to evaluate the intensity of certain signs and symptoms that arose when they were exposed to the stimuli from the series A, B, and C. For the evaluation of these signs and symptoms, a questionnaire with the following items was used: a) do you feel your mouth full of saliva?, b) do you feel your nose full of mucosa?, c) are your eyes watery?, d) do you want to yawn?, e) do you feel discomfort in your kidneys?, f) do you feel your stomach's contracting?, g) do you feel chills?, h) are you shivering?, i) is your heart beating quickly?, j) are you muscles stiffening?, k) do your muscles hurt?, l) do your bones hurt?, m) do your joints hurt?, n) do you feel discomfort in your belly?, o) do you feel nauseous?, p) do you feel like you have diarrhea?, q) do you feel sweaty?, r) do you have goose pimples?, s) do you notice any changes in respiration? Reliability and validity were made prior to this study with different participants (42 addicted persons, 23 men and 19 women) to those participating here. Reliability rate in this questionnaire was 0.89, calculated by the two meddles method with Spearman-Brown correction. Cronbach's Alfa coefficient was 0.88. Criterion validity (predictive validity) was obtained by applying a concurrent validity design, and reached a value of 0.77. The criterion was obtained by interviewing participants with similar characteristic to those participating in the present research and under the same stimuli conditions. Each participant was interviewed by two researchers, with an agreement level, obtained through Cohen's Kappa coefficient, of 0.81. Participants had to mark from 0 to 10 for each question, knowing that

zero meant «not at all» and ten meant «greatly». Each participant answered the above questions before and after presentations of the stimuli that composed the distinct stimulus series. The points representative for each participant at each moment of evaluation were obtained by calculating the arithmetic mean of the assigned points of each of the 19 experimental questions.

Apparatus

The different stimulus images (NSs, CSs, and flashes of white light) were presented using a projector. The stimuli were projected onto a screen, 150 cm x 100 cm, located in front of the participant at a distance of three meters. The recording of the physiological variable was carried out through use of a Letica polygraph, model Leti-Graph 2000, with two recording channels on paper and a thermal pen. To detect the electrodermal activity, two bipolar electrodes with silver chloride capsules (Ag/AgCl), Letica model TRS 75, with a contact area of 1 cm^2, located at the second segments of the index and middle fingers of the left hand was used. As contact medium, an electrolytic gel with a concentration of 0.05 molar of ClNa (equivalent to 0.29 grms. per 100 ml. of water) was used. During recording of the electrodermal activity, speed of paper advance was 2mm/sec. Computer controlled the presentation and duration of the stimuli, as well as the recording of the response. As such, an input-output DIG 720 card, from Med Associates, INC controlled the polygraph event marker and the slide projector, through an electronic interconnection relay built for this purpose. The card was in a computer loaded with all the necessary control programs. These were written in Turbo Basic (computer language). During the entire session, the participants wore Ross headphones, model RE-223, through which they listened to a background noise of a 20-decibel intensity produced by the CPU (central processing unit) of the computer.

Procedure

Before each session, the participants detoxified of heroin underwent a drug analysis test for the detection of opiates in the urine. ONTRAK, from Roche Diagnostic Systems, was the detection Kit used for this purpose. If de result was negative, the session continued. This system of analysis was selected became of its great versatility and reliability (100% efficacy in the detection of opiate substances). This system results in an extremely high (+) correlation with methods using gas chromatography and spectrometry of mass. To control for environmental artifacts, the physical conditions of the experimental chamber, where all physiological and subjective variables were measured, were held constant throughout the sessions and for all participants. Thus, the experiment was carried out in a sound proof, odorless chamber, with the temperature ranging from 20 to 25 degrees centigrade (68 to 77 degrees Fahrenheit), and illuminated with a pale light of 10 watts. The variable electric fields of the room were controlled by grounding the participants. Additionally, during the entire session, the researcher noted on paper any extraneous incidents observed: noise, movements, coughing, etc., with visual and auditory access from outside the chamber, as well as to surrounding area.

Design

Comprehensively, the research design was an independent groups with repeated measures across all participants (in each group), such that all participants in the study experienced all the stimuli that constituted the stimulus series (SSA, SSB, SSC). Thus, for all participants in both the CG and the EG, the C response was measured in the presence of each of the four stimuli that formed the stimulus series A, B, and C, thus obtaining four values for physiological variable for each participant and series. Also, the SAS response was measured before and after the stimulus series A, B, and C. The order of presentation of the three stimulus series (SSA, SSB, SSC) was assigned in an incomplete counterbalance format, resulting in six sequences, each one of these composed of the same previous stimulus series, but ordered differently. The 48 participans in the study (24 from the CG, 24 from the EG) were divided into 12 distinct groups, each one with two men and two women. To specify, each one of the 12 groups passed through a sequence of stimulus series that another group had already experienced, given that there were only six sequences used (from the incomplete counterbalance). Additionally, it is to be noted that of the two men and two women in each (of the 12) groups, one man and one woman were from the CG, and one each from the EG. The physiological variable, C in the presence of both the neutral and conditioned stimuli, was studied by means of a mixed factorial design. Here, the factor termed Group was divided into two levels: one level called «control group» (CG), the second one called «experimental group» (EG). The factor Sex was also made of two independent groups, and divided into two levels: «men» and «women». The factor Stimulus Series was the repeated measures factor, and was manipulated within subjects at three levels: a first level termed «SSA», a second level «SSB», and a third level termed «SSC». Finally, the factor termed Stimulus was, as the previous one, of repeated measures, and used within subjects manipulations at four levels: «S1», «S2», «S3», «S4». To be precise, the neutral and the conditioned characteristics of the stimuli that made up each of the levels of the factor Stimulus changed according to the stimulus series in which these stimuli were found. The subjective variable SAS was studied through a mixed factorial design. The factors Group and Sex were independent groups, each manipulated at two levels: «CG» and «EG», and «men» and «women», respectively. The factor Stimulus Series was a repeated measure, with within-subject manipulations at three levels: «SSA», «SSB», and ASSC». Finally, the factor Moment of Evaluation was likewise a repeated measures factor, with intra subject manipulations at two levels: a first level termed «before the stimulus series» (PRE), and the second level termed «after the stimulus series» (POST).

Statistical analysis

First, using a 2x2(x4x3) ANOVA, the values for C from both the CG and EG were analyzed, taking into account the two levels of the Sex factor, in the presence of each of the four stimuli that composed the stimulus series A, B, and C. Next, using a 2x2(x3x2) ANOVA, the values of SAS from both, the CG and EG were analyzed, taking into account the two levels of the Sex factor, before and after the presentations of the stimulus series A, B, and C. With the factors that were manipulated between

groups, a $p < 0.05$ was used when determining level of significance. A $p < 0.01$ was used when analyzing the within-subject factors. To adjust the degrees of freedom in the repeated measures factors, the Greenhouse-Geisser Epsilon correction (GG) was applied. However, the results are reported with the original degrees of freedom and the corrected probability values.

Results

After conducting the statistical analysis of the data, it was seen that there was no effect of the factor Sex. Because of this, and to simplify the figures of the resulting data, the Sex factor was omitted.

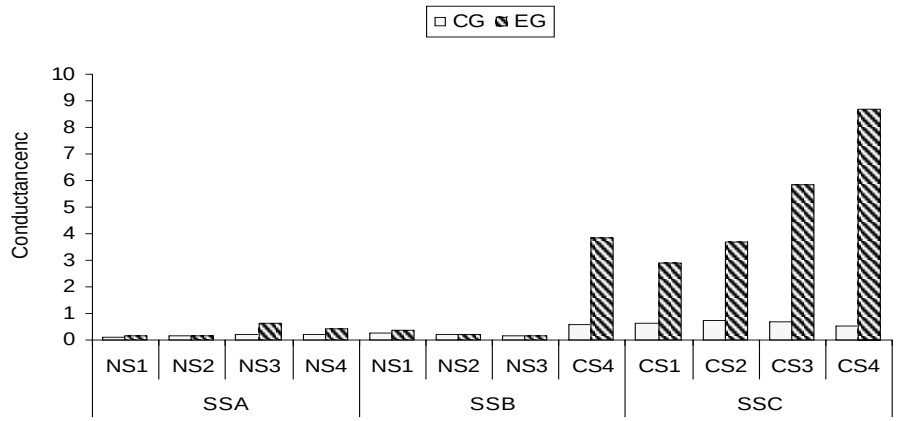
Conductance (C)

The results of a 2x2(x3x4) ANOVA showed statistically significant main effects of the Group factor ($F(1,44)=161.06$, $p<0.01$), the Series Stimulus factor ($F(2,88)=232.72$, $p<0.01$; $GG<0.008$), and the Stimulus factor ($F(3,132)=151.94$, $p<0.01$; $GG<0.006$). Additionally, there was a statistically significant interaction effect of the three above-mentioned factors ($F(6,264)=35.18$, $p<0.01$; $GG<0.004$). No significant effect of the Sex factor was observed; neither was there a significant interaction effect of this factor with the previous three factors. Also shown are the results of the «a priori» comparisons in an analysis of the Group x Stimulus Series x Stimulus interaction, in both CG and EG, in the presence of the NSs and the CSs in the stimulus series A, B, and C (SSA, SSB, SSC). The results do not show significant effects of the stimuli in the stimulus series for the CG. The same is true for the stimuli of stimulus series A for the EG. However, significant effects were seen with the stimuli in SSB in the EG ($F(3,69)=92.23$, $p<0.01$; $GG<0.002$). That is, statistically significant differences were found in comparing NS1 with CS4 ($F(1,23)=89.15$, $p<0.01$), NS2 with CS4 ($F(1,23)=90.26$, $p<0.01$), and NS3 with CS4 ($F(1,23)=96.21$, $p<0.01$). With the EG participants the rest of the comparisons did not yield significant differences. Also, a significant effect was found in the stimuli of SSC in the EG ($F(3,69)=52.38$, $p<0.01$; $GG<0.007$). Significant differences were seen in comparing CS1 with CS2 ($F(1,23)=16.81$, $p<0.01$), CS2 with CS3 ($F(1,23)=26.91$, $p<0.01$) and CS3 with CS4 ($F(1,23)=17.22$, $p<0.01$). Significant differences were found in comparing the CG with the EG after the presentation of CS4 in SSB ($F(1,47)=72.56$, $p<0.01$) and after presenting, in SSC, CS1 ($F(1,47)=72.13$, $p<0.01$), CS2 ($F(1,47)=103.76$, $p<0.01$), CS3 ($F(1,47)=123.11$, $p<0.01$), and CS4 ($F(1,47)=155.27$, $p<0.01$). However, no significant differences were found between the CG and the EG after presenting NS1, NS2, NS3, or NS4 in SSA; neither after presenting the NS1, NS2, or NS3 in SSB. Of particular interest is the result showing that the EG participants responded with larger increments in C in the presence of the CS with more stimulus elements (CS4), when this was preceded by other CSs, than when preceded by NSs. Thus in the EG persons, significant differences were found between the CS4 in SSB and the CS4 in SSC ($F(1,23)=30.20$, $p<0.01$). This was not so in the CG participants (see Table 1 and Figure 1).

TABLE 1. Means (M) and Standards Deviations (SD) of the magnitude of conductance response (micromhos), in the Control and the Experimental Groups (CG, EG), to effects of stimuli that comprised the stimulus series A, B, and C (SSA, SSB, SSC).

		SSA				*SSB*				*SSC*			
		NS1	NS2	NS3	NS4	NS1	NS2	NS3	CS4	CS1	CS2	CS3	CS4
CG	M	0.12	0.14	0.19	0.2	0.24	0.19	0.15	0.59	0.63	0.72	0.66	0.51
	SD	0.19	0.17	0.08	0.31	0.15	0.1	0.12	0.13	0.25	0.32	0.24	0.29
EG	M	0.18	0.17	0.62	0.42	0.36	0.22	0.18	3.83	2.92	3.7	5.84	8.7
	SD	0.16	0.18	0.37	0.2	0.13	0.08	0.11	0.99	0.7	0.92	1.13	1.16

FIGURE 1. Effects of the stimuli that comprised the stimulus series A, B, and C (SSA, SSB, SSC), on the magnitude of the conductance response (micromhos), in the Control and the Experimental Groups (CG, EG).

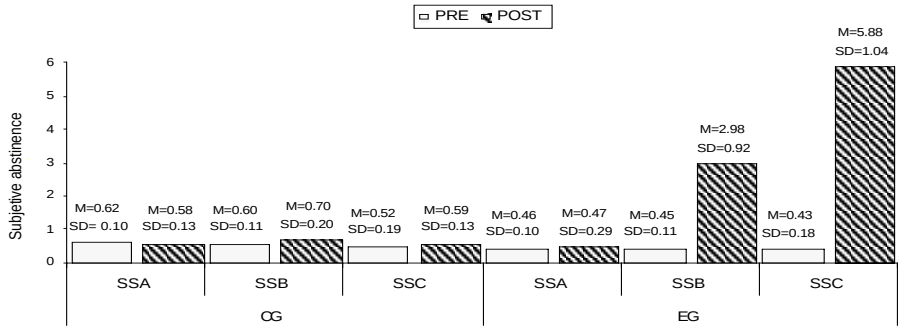


Self-perception of abstinence symptoms (SAS)

The results of a 2x2(x3x2) ANOVA showed significant effects of the Group factor ($F(1,44)=165.22$, $p<0.01$), Stimulus Series factor ($F(2,88)=136.21$, $p<0.01$; $GG<0.006$), and Moment of Evaluation factor ($F(1,44)=170.77$, $p<0.01$). Additionally, there was a significant Group x Stimulus Series x Moment of Evaluation interaction effect ($F(2,88)=75.51$, $p<0.01$; $GG<0.004$). No significant effect was found in the Sex factor or in an interaction of Sex with the three above factors. Next, shown are the results of «a priori» comparisons in an analysis of the Group x Stimulus Series x Moment of Evaluation interaction, in both CG and EG, before and after the stimulus series A, B, and C (SSA, SSB, SSC). Significant differences were found in the EG participants, comparing the values of SAS obtained before the SSB ($F(1,23)=65.78$, $p<0.01$), and the

SSC ($F(1,23)=186.16$, $p<0.01$). This was not so in the SSA. However, this was not the case in the CG participants across the above-listed stimulus series. Also, significant differences were seen between CG and EG, after SSB ($F(1,46)=30.59$, $p<0.01$), and after SSC ($F(1,46)=210.76$, $p<0.01$). No significant differences were found in the SAS values, in CG or in EG participants, before the stimulus series A, B, and C, nor in the values obtained for CG participants after these series. In contrast, significant differences were found in the EG after these above-listed series ($F(2,46)=157.89$, $p<0.01$; $GG<0.005$). Thus, in EG significant differences were seen in comparing the SAS values obtained after SSA with those obtained after SSB ($F(1,23)=68.91$, $p<0.01$), and those obtained after SSB with those after SSC ($F(1,23)=163.09$, $p<0.01$) (see Figure 2).

FIGURE 2. Subjective response of abstinence (0-10), before (PRE) and after (POST) presentation of stimulus series A, B, and C (SSA, SSB, SSC,), in the Control and the Experimental Groups (CG, EG).



Discussion

One might think that the persons addicted to heroin, even having been detoxified from this substance, come to emit (under control of certain drug-related stimulus conditions) anticipatory CRs, at the electro-dermal level (increases in skin electrical conductance) opposite to those unconditioned responses induced by this opiate in this one physiological system (decreases in skin electrical conductance). Therefore, in the addicted persons, the magnitude of those responses was greater in the presence of the last stimulus of the series of CS compounds, ordered from least to most in number of conditioned stimulus elements, than in the presence of a single CS compound (even if this contained more stimulus elements). Regarding the subjective responses of SAS, it was observed that the detoxified addicted persons showed values significantly higher in the presence of CSs than those showed by the non-addicted persons in the presence of the same CSs. According to these data, it may be that the CSs, while evoking certain CRs of physiological disequilibrium (CCRs to the effects of heroin) were favoring the development of interoceptive stimuli and that, these being self-perceived by the person,

were interpreted as sings and symptoms of abstinence. That is, signs and symptoms of abstinence, could acquire the function of discriminative stimuli (stimuli that set the occasion for a given response that will result in a given reinforce) that raise the probability, at least in part, of emission of personal responses of craving responses for the drug, and perhaps also, explicit responses of drug searching, administration, and thus of relapse into abuse of the drug, under control by a negative reinforcement mechanism. As such, the detoxified person would desire heroin and emit behaviors of drug administration, at least in part, in order to escape the organically perceived discomfort. To resume, one might think, even at the expense of succumbing to an excess of generalization of the results of this study, that the levels of heroin craving that some detoxified addicts show for this substance, as well as the probability that they have of relapse into drug use, may be due, in part, to mechanisms of negative reinforcement that seemingly, and according to the given data are set in motion under control of certain pre-drug CSs.

Along general lines, to interpret the meaning of the results obtained one can say, at least, that with the addicted persons who participated in this study, with the given stimulus material, and with the established methodology, it was possible to detected certain CRs, in the response systems evaluated, opposite to the effects that the heroin induces in an unconditioned manner. In other words, in the presence of CSs, responses of electrodermal hyperactivity (increases in the skin electrical conductance) and subjective responses of SAS was detected. As such, it was observed in this study what could be termed, according to the model of the environmental specificity of the conditioned abstinence syndrome.

Reviewing the work carried out with humans in this area of research, one can see that some of the results obtained in the present study corroborate those obtained previously by different authors at different times. It is also possible that other results, while extremely novel, could supply new evidence in support of the model here conceptualized. For example, various authors detected subjective responses of desire for heroin and SAS in the presence of certain predrug CSs (Childress *et al*., 1993; Childress *et al*., 1986; Legarda, Bradley, and Sartory, 1987, 1990; Trujillo, 1997). Others detected increases in conductance values (Childress *et al*., 1993; Sideroff and Jarvik, 1980a, 1980b; Ternes, O'Brien, Grabowski, Wellerstein, and Hordan-Hayes, 1980).

Some of the novel results obtained in this study that could supply new evidence in favor of the environmental specificity of abstinence model in humans were: a) the detection of a stronger evocative power of CRs of abstinence by sequences composed of various CSs compounds than by a single CS compound; and, b) the detection of a lack of necessity, on the part of the addict, of expectations of drug availability for the CRs of abstinence to arise.

STUDY 2

This study was done six weeks after the study 1. The aim was to detect, in the presence of certain CSs related to heroin, CRs mimetic to the direct subjective effects produced by this drug in an unconditioned form. Basically, the study consisted in

presenting live to detoxified persons visual and tactile stimuli related to the ritual of heroin administration (the «pump» act without drug), supposedly associated with the direct effects of the drug through the place they hold in the behavioral chain of addiction. The dependent variable measured was SAS.

Method

Participants

The participants of this study were the same as the experimental group (EG) in study 1.

Stimulus materials

Two different stimuli were used: a) a slight needle prick administered by the researcher in the area about where the participant used to inject himself in the past, using a disposable hypodermic needle very different from the type used during the heroin use; b) a stimulus complex composed of visual and tactile elements pertaining to the behavioral chain of drug self-administration. That is, the participant performed the ritual of «pump» without the drug for 30 seconds, using a hypodermic needle and an insulin-type syringe like those commonly used for heroin administration, in the same point of the arm where the drug had been injected in the past. Both the needle and the syringe were disposable. These stimuli were temporally organized within the stimulus series A, B, and C (SA, SB, SC). The stimulus order that formed each series was as follows: SA, a) five minutes of adaptation to the experimental room where the variables were recorded during which the participant remained alone, b) three minutes of control condition; SB, a) five minutes of adaptation to the experimental room where the variables were recorded during which the participant remained alone, b) three minutes and administered the needle prick by the researcher 30 seconds before the end of this period; SC, a) five minutes of adaptation to the experimental room where the variables were recorded during which the subject remained alone, b) three minutes, while the participant performed the «pump» ritual during the last 30 seconds of this period.

Dependent variable: *Self-perception of abstinence symptoms (SAS)*

This was used as an indication of subjective perception of abstinence. Various physical-bodily symptoms similar to those that appear in the syndrome of organic withdrawal from heroin were evaluated in a questionnaire-like form, 19 different questions in total, as in study 1. The participants had to self-evaluate these symptoms before the five minutes of adaptation prior to the stimulus series A, B, and C and after the stimulus series. The scale of points ranged from 0 to 10 for each question, with 0 meaning «not at all» and 10 meaning «very much». The representative score for each participant in each moment of evaluation was obtained by calculating the arithmetic mean of the scores assigned to each of the 19 questions.

Apparatus

Recording of the subjective dependent variable was done using the same questionnaire as the study 1.

Procedure

Each participant individually went through three sessions in three successive days, that is one session per day. The first moments were used to create a relaxed environment between the participant and the researcher. Next, urine analysis using the Ontrak «Kit», as in study 1, was performed for the detection of opiates. The physical conditions of the experimental room were kept constant during the sessions for each participant, as described in study 1.

Design

The experimental design used two independent groups (12 men, 12 women) with multiple replications across participants so that each was exposed to the stimuli complexes in the three stimulus series A, B, and C. The response SAS, was measured before and after each stimulus series. The order of presentation of the stimulus series was balanced, resulting in six different sequences each consisting of the three stimulus series but in different orders. Each of these six sequences was presented to six different groups of four persons each, so that each series of the three that formed each sequence was presented to the participants in a different day. Each of the six different groups of four persons was formed by randomly distributing the 24 participants of the study.

Statistical analysis

The values of SAS obtained for the groups' men and women before and after the three stimulus series were analyzed using an ANOVA 2(x3x2). The level of significance in the factors manipulated between groups was set at 0.05. The level of significance for the factors manipulated within subjects as well as for the interaction between groups and within subject factors was 0.01. To adjust the degrees of freedom in the repeated measure factors the Greenhouse-Geiser epsilon correction was applied. However, the results are presented with the original degrees of freedom and the corrected values of probability. After conducting the statistical analysis of the data, it was seen that there was no effect of the factor Sex. Because of this, and to simplify the figures of the resulting data, the Sex factor was omitted.

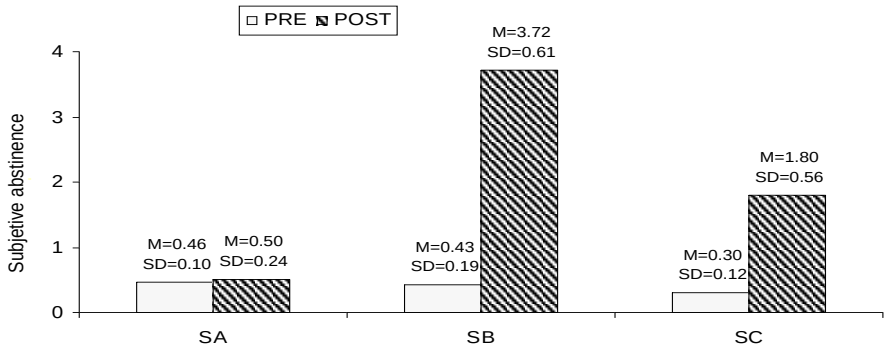
Results

Self-perceptions abstinence symptoms (SAS)

The results of the ANOVA 2(x3x2) showed statistically significant effects of the factors Stimulus Series ($F(2,44)=25.43$; $p<0.01$) ($GG<0.006$) and Moment of Evaluation ($F(1,22)=150.33$; $p<0.01$), as well as for the interaction of these two ($F(2,44)=70.21$; $p<0.01$). However, there were no significant effects of Sex or the interaction of this factor with the former two. The analysis of the interaction Stimulus Series x Moment of Evaluation showed values significantly greater after the needle prick by the researcher

(SB) than after control condition (SA) ($F(1,23)=83.81$); $p<0.01$) and greater than the values obtained after the «pump» ritual (SC)($F(1,23)=34.18$; $p<0.01$). The results showed statistically significant differences between response values after control condition (SA) compared to those with given after the «pump» ritual without the drug (SC) ($F(1,23)=36.50$; $p<0.01$). Additionally, there were significantly greater values of SAS after stimulus series B ($F(1,23)=258.43$; $p<0.01$) and series C ($F(1,23)=141.17$; $p<0.01$) than those seen before these stimulus series. No significant differences were seen between the values obtained before or after the control condition, SA (see Figure 3).

FIGURE 3. Response of subjective abstinence (0-10) before (PRE) and after (POST) of control condition (SA), before and after the needle prick (SB), and before and after the «pump» ritual without the drug (SC) in detoxified addicted participants.



Discussion

Regarding the subjective response of SAS, it was seen that the participants demonstrated significantly greater values after the needle prick (SB) than those seen after control condition (SA) and after the «pump» ritual (SC). Perhaps, this might be expected if one considers that the participant sequentially received one nociceptive stimulus (needle prick). This could have occasioned a level of activation sufficiently high for him/her to self-perceive a relative state of organic disequilibrium that, in its turn, could have unleashed certain responses of abstinence. It was seen that SAS response was greater in SB than SC. This might be expected by the temporal proximity of "pump" ritual (CS) with the unconditioned effects of the drug after its administration. Perhaps, this might be considered as subjective CRs mimetic to the unconditioned effects of the heroin.

General discussion

One important aspect to be examined in this section is that concerning the arguments made by different researchers in relation to some of the problems thus far not resolved in this area of research. Along this line, it is possible to believe that the difficulty in detecting CCRs (conditioned abstinence) could be due, according to the opinion of King, Bouton, and Musty (1987), to the fact that these responses are more difficult to evaluate than the environmental specificity of tolerance. Other researchers (Hinson and Rhijsburger, 1984; Poulos and Hinson, 1984), in the face of this dilemma of the non-detection of CCRs, think that it is not possible to evaluate these responses in certain systems of response because, in the absence of the effect of the drug, they are attenuated by mechanisms of homeostatic regulation, that is, by the lack of pharmacological preparation of the system that occasions the compensatory-type anticipatory CRs. From this standpoint, it is possible to think that the detection or non-detection of these responses might not depend so much on the presence of the drug's effect (pharmacological preparation of the system of response) as on the method used to evaluate these responses. However, what might actually be the case is that the non-detection of CCRs to the effects of the drug is due to the lack of stimulus generalization from the context where the responses were acquired to the context where they are being evaluated (Siegel, 1988). For this reason, when designing studies for the detection of this kind of response class, it is necessary to be exceptionally meticulous in selection of the materials to be used and their manipulation.

On the other hand, authors like Goudie and Griffiths (1986) state that the fact of not detecting, at times, CCRs to the effects of the drug and the fact, as well, of not observing these responses when the phenomenon of environmental specificity of tolerance occurs might indicate that such responses are not components of the phenomenon of associative tolerance. These authors believe that the exceptions in the detection of compensatory CRs might be characterized as the «Achilles heel» of the model of conditioned tolerance. What probably should be considered is that the problem is not in the model, despite the dilemmas it presents, but in the method that is sometimes followed to empirically assay the tentative predictions made within the model's framework. For the moment, this model can explain the results obtained in the present work within an associative-type comprehensive paradigm, something that is not possible with the model of tolerance as habituation.

Nevertheless, it must be made explicit that one should not negate the future possibilities of the ideas defended from the viewpoint of the comparative theory of habituation, characterized as such by Mackintosh (1987). Neither should one discard the utility of the model of tolerance as habituation, since it is necessary to consider, as do other researchers (Baker and Tiffany, 1985), that this model could be of great relevancy for understanding tolerance to drugs, if from within its framework one can make valuable predictions regarding the environmental specificity and extensions thereby. However, from this work's perspective, that model does not take into account the CRs of abstinence as something underlying tolerance despite the high correlation that exists between both phenomena (Hinson and Siegel, 1983). Besides, to reiterate what Mackintosh stated (1987), it is possible to think that the empirical data obtained through that model

present more problems of interpretation than do those seen in the model of conditioned abstinence.

In a global manner, perhaps the CRS opposite (CCRs) to the effects of heroin emitted by the detoxified subjects, with the CSs of the study, were due to the establishment during their histories of addiction of a strong association between these stimuli and the stimuli of the state of abstinence through which they have passed. Therefore, these CRs might be considered as empirical evidence in support of the existence of conditioned abstinence.

It might be that these CSs, while evoking certain CRs of physiological disequilibrium (CRs compensatory to the effects of heroin), were favoring the development of interoceptive stimuli and that, being perceived by the subject, were interpreted as signs and symptoms of abstinence capable of bringing about responses of desire for heroin. That is, the detoxified subject would desire heroin and would respond by drug administration to reduce the perceived organic discomfort. However, this would be a very simplistic model that states that a detoxified addict would desire heroin and relapse into its use just because of this supposed negative reinforcement mechanism, when it is known that in every addictive behavioral process mechanisms of positive reinforcement maintained by the gratification of the drug also control the behavior. Additionally, other relevant factors are involved such as, for example, response cost of change to behavioral alternatives (Nureya, 1985), factors related to the making of decisions under ambiguous stimulation (De la Fuente, Trujillo, Ortega, Martin, and Estarelles, 1993), factors of learning about self perception of interoceptive stimulation (Lubinski and Thompson, 1987), etc.

The results obtained in this work, together with those from other research, can serve as factors to consider when designing strategies for the treatment of heroin addiction that would be more precise than those in existence. Thus, perhaps the efficacy of the programs for the treatment of heroin addiction could be bettered, at least in part, if one considered for the structure of the program that these given phenomena could easily be under specific contextual control. Therefore, there may be important elements to consider for the optimization of the results when an addict is detoxified and reinstated in his/her daily environment. One must remember that there will be certain conditioned stimuli in this environment with the capacity intact to evoke in this type of subject CRs of tolerance and/or abstinence, and that these responses, in their turn, could be controlling factors with enough specific power to facilitate the maintenance of the addictive behavioral chain.

Lastly, it is important to state that these responses of conditioned tolerance and/or abstinence (CCRs) might be involved in the development and maintenance of the following clinical phenomena: a) the need for the addict to increase the dose of the drug in order to obtain a stable effect of this substance, after successive administration; b) the relapse of addicts, after having been detoxified, under control of the mechanism of negative reinforcement; c) certain effects of overdose when administering the substance in novel settings. As such, the responses mimetic to the effects of heroin (MCRs) might contribute, also, to the development and maintenance of the following clinical phenomena: a) the increase in the power of the gratifying effect of heroin, and the resulting frequency

of its use; b) certain effects of overdose when increasing the effect of the substance; c) the phenomenon termed «fantasy of the needles» (the addict performs the injection ritual without the drug, receiving effects similar to those produced by the substance in an unconditioned form); and d) the placebo phenomenon.

To conclude, in relation to the factors of control that underlie the development and maintenance of the anticipatory CRs, it is possible to think that the direction of these responses will depend on the form and moment in which the associations between the contextual stimuli and their effects take place. Perhaps, it is wise to consider that the direction and intensity of the CRs anticipatory to the effects of heroin might be a function of the intensity of the biological effect of the drug and, additionally, of the form and moment in which the multiple interactions between the mediating variables in the addictive history of each subject occur. In other words, the determining conditions of the direction of the anticipatory CRs might be seen in the multiple interactions between the different states through which an addict passes before, during, and after administration of the drug throughout his/her history of consumption and the stimuli that are present at each moment.

Regarding future research endeavors, it will be important to conduct studies for the identification of the functional relations between anticipatory CRs (mimetic and compensatory) and drug relapse. To accomplish this, a greater number of modalities of physiological response will be measured using telemetric techniques, with longer periods of recording and in the habitual context of the addict. Perhaps, in this manner, it will be possible to make contact with effects that are barely accessible in the laboratory, and it will be easier to clarify the true clinical dimension of the phenomena discussed above.

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