

EFFECT OF ADDICTIVE HISTORY ON THE DIRECTION OF CONDITIONED RESPONSES ANTICIPATORY TO THE EFFECTS OF HEROIN*

Humberto M. Trujillo
University of Granada

The object of this study was to examine the direction and intensity of the anticipatory conditioned responses of mimetic character (conditioned sensitivity) and of compensatory character (conditioned abstinence) to the analgesic and subjective effects of heroin. There were four different groups, 16 men in each: G1, non-addicts; G2, occasional users; G3, non-detoxified addicts; G4, detoxified addicts. The responses, heart rate (HR), electrodermal activity (EA), desire for heroin (HD), withdrawal symptoms self-perception (WSS), and subjective symptoms mimetic to those induced by heroin (SMS) were evaluated before and after the projection of two films, one with neutral stimuli, the other with heroin-related stimuli. Before the end of each film, an electric shock (ES), 4 mA in intensity and 2 seconds in duration, was administered. Compensatory conditioned responses to the effects of heroin were seen in G3 and G4, and mimetic responses in G2 ($p < 0.01$). These results are discussed in the context of the environmental specificity model of anticipatory responses to the effects of heroin.

El objetivo de este estudio fue analizar la dirección y la intensidad de las respuestas condicionadas anticipatorias de tipo mimético (sensibilización condicionada) y compensatorio (abstinencia condicionada) de los efectos analgésicos y subjetivos de la heroína. Se trabajó con cuatro grupos distintos de sujetos, cada uno de los cuales estaba formado por 16 hombres: (G1), no adictos; (G2), consumidores esporádicos (G3), adictos no desintoxicados; (G4), adictos desintoxicados. Las respuestas de tasa cardíaca (TC), actividad electrodérmica (AE), deseo por la heroína (DH), autopercepción de síntomas de abstinencia (ASA) y síntomas subjetivos similares a los que induce la heroína (ASM) se evaluaron antes y después de la proyección de dos películas, una con estímulos neutros y otra con estímulos relacionados con la heroína. Antes de finalizar cada una de las películas se administró un choque eléctrico (CE) de 4 mA de intensidad y 2 seg. de duración. Se detectaron RCs compensatorias de los efectos analgésicos y subjetivos de la heroína en los grupos G4 y G3, y miméticas en el G2 ($p < 0.01$). Los resultados se discuten en el contexto del modelo de la especificidad ambiental de las respuestas anticipatorias de los efectos de la heroína.

Apparently, effects of drugs may be somehow modulated by non-pharmacological factors (Childress et al, 1993; Hinson and Siegel, 1983; King, Joyner and Ellinwood, 1994; Pavlov, 1927; Schwart-Stevens and Cunningham, 1993; Thompson and Ostlund, 1965; Wikler, 1948, 1973a; 1973b). That is, the result of chemical stimulation caused by different drugs appears to be not only dependent on pharmaco-kinetic and pharma-

co-dynamic principles, but also on the experience in using the substance in a specific context where, probably, Pavlovian-like stimuli association mechanisms mediate.

In general terms, behavioural theories referring to intensity and direction of responses evoked by stimuli associated with the effects of opiates fundamentally argue for two global hypotheses concerning the effects of such stimuli in response systems belonging to organisms which are biologically detoxified of these drugs. A first hypothesis supports that certain stimuli associated with withdrawal effects and/or with biological responses of homeostatic regulation of neurochemical action of morphine components may evoke conditioned

The original Spanish version of this paper has been previously published in *Psicothema*, 1996, Vol. 8 No 3, 475-489

.....
*Correspondence concerning this article should be addressed to Humberto M. Trujillo. Departamento de Psicología Social y Metodología de las Ciencias del Comportamiento. Facultad de Psicología. Universidad de Granada, 18071 Granada. Spain.

responses of tolerance and/or withdrawal (Childress, McLelland and O'Brien, 1987; Childress, McLelland, Natale and O'Brien, 1987; Grabowsky and O'Brien, 1981; Hinson and Siegel, 1983; Trujillo and De la Fuente, 1994; Trujillo, 1994, 1995; Wikler, 1973 a, b and 1980). That is, CRs that are compensatory of the opiates' unconditioned effects.

In a second hypothesis it is tentatively predicted that these CSs of the drug may elicit mimetic CRs of the unconditioned effects induced by opiates (Lett, 1989; Levine, 1974). That is, some of these responses may mimic, rather than compensate, such effects. In a similar way to what happens with tolerance and withdrawal CRs, in the mimetic CRs of heroin's unconditioned effects, associative conditioning mechanisms may be mediating (Trujillo, 1992).

However, there are very few studies made with humans which provide enough data consistent with the proposed hypothesis. This may be due to the difficulty of studying such phenomena (Ehrman, 1991; De Wit and Stewart, 1981). In summary, it appears that the mediating variables in these phenomena and the mechanisms organising them are largely unknown.

In synthesis, with respect to the direction of pharmacological CRs, we can frequently observe mimetic as well as compensatory CRs of the unconditioned effects of drugs. However, it is not yet clear what are the conditions favouring the appearance of each of these two types of response. Furthermore, with excessive frequency, research in this area has concentrated on asking whether CRs to heroin are opposed or similar to those unconditionally evoked by it, instead of asking in what framework of conditions there is a greater probability of the occurrence of one type or the other.

Researchers such as Obál, Viesay and Benedek (1976), or Eikelboom and Stewart (1982) have attempted to solve this problem. However, these authors do not explain why studies with animals, with the same contextual CSs and with the same drug mediating in the associative process, sometimes find compensatory CRs and other times CRs mimicking the drug's effects (Siegel, 1985); and, more specifically, why the same happens in humans organically detoxified from heroin (Trujillo, 1992, 1994). In other words, the mechanisms described by Obál et al and Eikelboom and Stewart do not appear to be of use as an explanatory basis for the intensity and the direction of the CRs that are anticipatory of the drug's effects.

The aim of this study was to analyse the direction and

intensity of anticipatory CRs produced by heroin-related stimuli in people with different addictive histories in comparison to subjective and analgesic effects of this drug. Special attention was paid to the analysis of anticipatory responses to the analgesic effects of heroin. This interest is based on Snyder's (1980) studies, in which the great power of the phenomenon of tolerance to heroin's analgesic effects is discussed. Basically, the procedure consisted in measuring a series of variables in the presence of an electric shock (ES), presumably of a noxious character, which was administered after the projection of a film with neutral stimuli (NSF), and after a film with conditioned stimuli belonging to the context and ritual of heroin consumption (CSF).

METHOD

Subjects

There were four different groups of subjects, each consisting of 16 men. The first group (G1) was comprised of people with no experience of opiate drugs. That is, non-addicted people with ages between 14 and 27 years, and a mean of 22.8, with a standard deviation of 3.52 years. The second group (G2) consisted of young people between 13 and 17 years of age, with a mean of 15.2 years and a standard deviation of 1.6 years; these youngsters had taken heroin only in a sporadic way. The third group (G3) was formed by addicts to heroin who habitually took this drug intravenously and were not detoxified; their ages ranged from 19 to 27 years of age, with a mean age 23.8 and a standard deviation of 2.8 years. The fourth group (G4) was comprised of detoxified heroin addicts with ages between 18 and 26 years, with a mean of 22.9 years and a standard deviation of 2.6 years. All the subjects in G4 had had direct experience with the drug through intravenous administration over a minimum 40-month period, and had gone many times through organic abstinence syndrome. These subjects, at the time of assessment, had already been detoxified from heroin for at least one month, and were under treatment with no medication at the *Centro Provincial de Drogodependencias* (Provincial Drug-addiction Centre) in Granada.

Stimuli

Two 30-minute video films were used. The film we refer to as CSF was made in the addicts' environment and contained a convincing story about the heroin "world", as well as all those stimulus elements proper to the real

consumption environment. The film NSF presented stimuli elements related to landscapes and birds. ES (electric shock) presented after the films was 4 mA in intensity and 2 seconds in duration. Presentation order of the two films was balanced.

Presentation sequence for both films and the ES was: (1) five minutes adaptation to the data registration room; (2) 30 minutes exposure to CSF or NSF (according to the balance order) and ES administration two minutes before the end of the projection; (3) 60 minutes break out of registration room; (4) five minutes adaptation to registration room; and (5) 30 minutes exposure to CSF or NSF (according to balance order) and ES administration two minutes before the end of the film.

Dependent variables

Heart Rate (HR)

Registration of this response was made by plethysmographically analysing the pulse through indirect photoelectric detection of changes in blood volume at finger level. Interval between pulses was transformed into HR (pulses per minute) expressed in real time pulse by pulse using a cardiac tachometer. Phasic activity was measured by analysing cardiac changes, second by second, after ES administration posterior to CSF and NSF. The cardiac activity change rate was obtained by subtracting the HR average value in the last 10 seconds of adaptation period preceding each film from the HR average value in the 20 seconds after ES administration in each film.

Electrodermal Activity (EA)

Skin electrical resistance values were registered and transformed into conductance (micro-ohms) for analysis. Conductance response amplitude on ES administration in both films was defined as the change in conductance from the beginning of the response until the point where it reaches its peak level.

In order to consider electrodermal responses as specific to the stimuli used, the following criteria were previously established.:

- a) amplitude of response change, measured in skin electrical resistance, should be greater than 0.5 Kilo-ohms.
- b) response should be initiated between one and six seconds after beginning of ES. This time range was established after the subjects' modal response latency value was identified.

Heroin Desire (HD)

A subjective indicator of the need for heroin was used. Subjects self-evaluated their desire for heroin on a 0-100 rating scale, where zero meant "absolute absence of desire" and 100 "very much desire". This evaluation was made on a specially-designed response sheet before and after presentation of NSF and CSF. Response change rate was obtained by subtracting the value obtained before the five minutes' adaptation prior to each film from the value obtained after ES administration posterior to each film. In order to facilitate statistical analysis, the scores in the 0-100 range scale were transformed into 0-10 range scores.

Withdrawal Symptoms Self-Perception (WSS)

This was used as a subjective, self-perceived withdrawal symptom indicator. Self-perceived intensity of some physical-bodily symptoms similar to those occurring in the organic heroin withdrawal syndrome was measured. That is, subjects had to self-evaluate WSS before the five minutes adaptation prior to NSF and CSF, and after ES administration posterior to NSF and CSF. In order to assess these signs and symptoms, a questionnaire was used which comprised the following questions: (1) Do you notice much saliva in your mouth? (2) Do you feel your nose to especially be mucous? (3) Are your eyes watering? (4) Do you feel like yawning? (5) Do you feel discomfort in your back? (6) Do you feel as though your stomach has shrunk? (7) Do you feel shivery? (8) Are you shaking? (9) Is your heart beating fast? (10) Are your muscles tight? (11) Do your muscles hurt? (12) Do your bones hurt? (13) Do your joints hurt? (14) Do you feel discomfort in your stomach? (15) Do you feel sick? (16) Do you feel as though you have diarrhoea? (17) Do you feel sweaty? (18) Do you have goose pimples? (19) Are you breathing heavily? Reliability rate in this questionnaire was 0.87, calculated by the test-retest method. Criterion validity (predictive validity) was obtained by applying a concurrent validity design, and reached a value of 0.77. Validation was made prior to this study with different subjects to those participating here. The criterion was obtained by interviewing subjects with similar characteristics to those participating in the present research and under the same stimuli conditions. Each subject was interviewed by two researchers, with an agreement level - obtained through Cohen's Kappa coefficient - of 0.81.

Subjects had to score from 0 to 10 on each question, with zero meaning "nothing at all" and 10 "very much".

The representative score for each subject at each point of the evaluation was obtained by working out the arithmetic mean of scores assigned to each of the 19 questions posed. WSS change rate in each film was obtained by subtracting each subject's WSS value obtained before the five minutes' adaptation prior to each film from the WSS value after ES administration in each film.

Self-Perception of symptoms mimetic to those caused by heroin effects (SMS)

Self-perceived intensity of some symptoms and bodily signs similar to the organic effects of heroin was measured. A questionnaire was used, which comprised the following questions: (1) Does your mouth feel dry? (2) Does your nose feel dry? (3) Do your eyes feel dry? (4) Does your stomach feel as though it is floating? (5) Do you feel hot? (6) Do your muscles feel relaxed? (7) Do you feel OK? In this questionnaire, reliability and validity rates were 0.70 and 0.59 respectively. The procedure for obtaining these coefficients was the same as that used for the WSS questionnaire.

Subjects had to score from 0 to 10 on each question, with zero meaning "nothing at all" and 10 "very much". The representative score for each subject at each point of the evaluation was obtained by working out the arithmetic mean of scores assigned to each of the 7 questions posed.

This response was evaluated before the five minutes' adaptation period prior to each film and after the ES administration which followed each of them. Response change rate for each subject and each film was obtained by subtracting the value obtained before the five minutes' adaptation prior to each film from the value after ES administration in each film.

Apparatus

A video player connected to a 26" TV monitor, placed 3 metres from the subject, was used to show the films. The film's sound track was presented through Ross RE-233 headphones.

Electric shocks (noxious stimuli) were administered by a bipolar armband in the inner part of subject's right arm. These were provided by Letica's Schocker LE 110 electric shock generator.

Physiological variables registration was made with a Letica Leti-Graph 2000 polygraph. Two amplifiers were connected to the polygraph in order to register cardiac activity (Letica's cardiometer amplifier CAR 300) and electrodermal activity (Letica's GSR 100 amplifier).

The recording of biological-physical pulse signal was made through Letica's photoelectric transducer TRU 300, placed at the first phalanx of the middle finger of the subject's right hand. Skin electrical resistance was measured using two Ag/AgCl cap bipolar electrodes, Letica's TRS 75, with a 1 cm² contact surface, placed at the second phalanx of the middle and index fingers of subject's left hand. Electrolytic gel was used as a contact medium, in a 0.05 CINa molar concentration (equivalent to 0.29 gr. per 100 ml of water). Advance speed of thermal paper was 2mm/sec.

Stimuli presentation and duration, as well as response registration, were computer controlled. That is, the polygraph events marker, video player and electric shock generator were controlled by a Med Associates Inc Output DIG 720 card, through a relayed electronic interconnection. The card was connected to an Amstrad PC 1512 DD computer in which the controlling programmes were run. These programmes were written in Turbo Basic.

Procedure

Subjects from G4 (detoxified from heroin), G3 (non-detoxified) and G2 (sporadic consumers) were submitted to analysis for qualitative detection of opiates in urine before the assessment session. The reactive kit used was Ontrak, by Roche Diagnostic Systems. This system of analysis was selected for its great versatility and reliability (100% effective for detecting opiate substances). Results with this system show a high correlation with those from gas chromatographic methods and mass spectrography.

For the control of environmental artefacts the physical conditions in the subjects' chamber were kept constant throughout the assessment sessions and for every subject. The procedures were carried out in a soundproof, odourless room with a temperature range between 20 and 25 degrees Centigrade, dimly lit by a 10-watt bulb. Control over variable electric fields in the room was made by earthing the subjects. In addition, the researcher wrote down on the polygraph paper roll any relevant event that occurred: noise, movements, cough, etc.

Design

The research design was one of independent groups (G1, G2, G3, G4) with intra-subject replication, so that every subject participating in the study was exposed to NSF and CSF, as well as to ES after each of them. Interesting variables (HR, EA, HD, WSS, SMS) were measured for

each subject in the way and at the time previously described, hence obtaining five values - one for each variable measured - for the dependent variable for each subject and film.

It should be made clear that presentation order of the films was balanced. That is, half of the subjects forming each group (eight subjects) were first exposed to NSF, had a 60-minute break, and were then presented with CSF. The other half of the subjects (the remaining eight) were first exposed to CSF, then rested for 60 minutes, and immediately afterwards were shown the NSF.

Statistical analysis

Each of the dependent variables (HR, C, HD, WSS and SMS) was analysed in a G (x E) factorial design by applying a 4(x2) ANOVA. In this design, the factor called G group was of an independent groups character and was manipulated by selecting four levels: G1, G2, G3, G4. In turn, Stimulus (S) was a repeated measures factor and manipulated intra-subjects with two levels: NSF and CSF.

In the present study a 0.05 inter-group significance level was used, and a 0.01 level in those factors manipulated intra-subject, and for the interactions between the two.

RESULTS

Heart Rate (HR)

4 (x2) ANOVA results showed significant effects of the Group ($F(3,60) = 36.04$; $p < 0.05$) and Stimulus ($F(1,60) = 58.24$; $p > 0.01$), as well as their interaction ($F(3,60) = 69.99$; $p < 0.01$) factors. Subjects in G4 showed HR change values significantly higher on ES after NSF ($F(1.15) = 75.89$; $p < 0.01$), and the same occurred with G3 subjects ($F(1.15) = 79.86$; $p < 0.01$). However, in G2

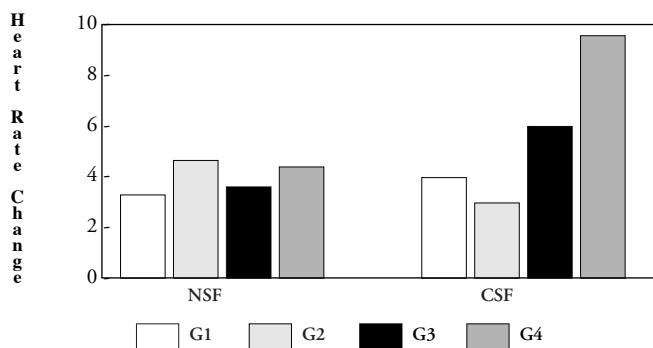


Figure 1: Effect of electric shock administered after the neutral stimuli film (NSF) and after context stimuli film (CSF) on heart rate change (pulses per minute) in non-addict subjects (G1), in sporadic consumers (G2), in non-detoxified addicts (G3), and in detoxified addicts (G4).

subjects, the opposite effect was found: that is, HR change values significantly lower on ES after CSF compared to those presented on ES after NSF ($F(1.15) = 62.48$; $p < 0.01$). With respect to G1, significant differences were not observed among change responses to ES after NSF and CSF. When comparing the four groups of subjects in the ES after CSF, significantly higher HR change values were observed in G4 than in G3 ($F(1.30) = 25.02$; $p < 0.05$), than in G2 ($F(1.30) = 94.87$; $p < 0.05$) and than in G1 ($F(1.30) = 68.58$; $p < 0.05$). Similarly, subjects from G3 showed higher HR change values than those in G2 ($F(1.30) = 66.55$; $p < 0.05$) and than those shown by G1 ($F(1.30) = 33.13$; $p < 0.05$). However, on comparing subjects from G2 and G1 it was observed that G2 subjects showed significantly lower HR change values than G1 subjects on ES after CSF ($F(1.30) = 11.44$; $p < 0.05$) (See Figure 1).

Conductance (C)

4 (x2) ANOVA results showed statistically significant effects of Group ($F(3,60) = 23.89$; $p < 0.05$) and Stimulus ($F(1,60) = 107.95$; $p < 0.01$) factors, as well as their interaction ($F(3,60) = 110.72$; $p < 0.01$). Subjects from G4 showed C values significantly higher on ES after CSF than after NSF ($F(1.15) = 241.66$; $p < 0.01$) and the same occurred with G3 subjects ($F(1.15) = 62.67$; $p < 0.01$). However, in subjects from G2 the opposite effect was observed; that is, C values significantly lower on ES after NSF ($F(1.15) = 39.42$; $p < 0.01$). With respect to G1, significant differences were not observed between responses to ES after NSF and CSF. When comparing the four groups in the ES after CSF condition, significantly greater C values were found in G4 than in G3 subjects ($F(1.30) = 121.49$; $p < 0.05$), than in G2 subjects ($F(1.30) = 355.89$;

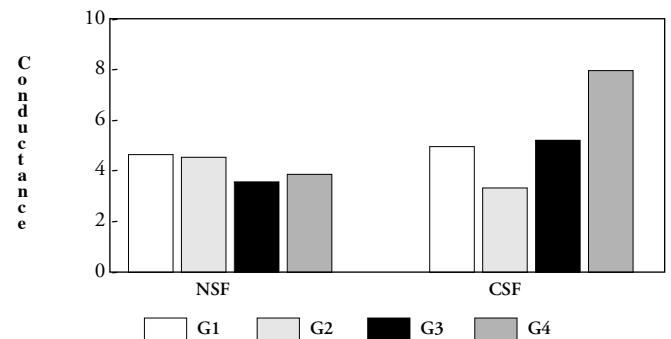


Figure 2: Effect of electric shock administered after neutral stimuli film (NSF) and after context stimuli film (CSF) on conductance amplitude response (micro-mhos) in non-addict subjects (G1), in sporadic consumers (G2), in non-detoxified addicts (G3), and in detoxified addicts (G4).

$p > 0.05$) and than in G1 subjects ($F(1,30) = 136.55$; $p < 0.05$). Also, G3 subjects showed significantly greater response amplitude values on ES after CSF than G2 subjects ($F(1,30) = 28.71$; $p < 0.05$). When comparing subjects from G2 with G1 it was observed that G2 subjects showed significantly lower C values than those shown by G1 subjects on ES after CSF ($F(1,30) = 18.17$; $p < 0.05$). Statistically significant differences were not found when G1 and G3 subjects were compared on ES after CSF (See Figure 2).

Heroin desire (HD)

4 (x2) ANOVA results showed statistically significant effects of Group ($F(3,60) = 284.14$; $p < 0.05$) and Stimulus ($F(1,60) = 652.56$; $p < 0.01$) factors, as well as their interaction ($F(3,60) = 257.39$; $p < 0.01$). Subjects in G4 showed significantly greater HD change values on ES after CSF than those shown after ES in NSF ($F(1,15) = 750.27$; $p < 0.01$), and the same occurred in subjects from G3 ($F(1,15) = 583.62$; $p < 0.01$) and from G2 ($F(1,15) = 139.66$; $p < 0.01$). With respect to G1, significant differences were not found among responses to ES after NSF and CSF. When comparing the four groups of subjects in ES after CSF condition, significantly greater HD change values were found in G4 than in G3 ($F(1,15) = 142.12$; $p < 0.05$), than in G2 ($F(1,15) = 201.00$; $p < 0.05$) and than in G1 ($F(1,15) = 96.68$; $p < 0.05$). Also, subjects from G3 showed significantly higher response change values than subjects in G2 ($F(1,15) = 23,65$; $p < 0.05$) or in G1 ($F(1,15) = 667.82$; $p < 0.05$). When comparing subjects from G2 with those in G1 it was observed that G2 subjects showed significantly greater response change values than those shown by G1 subjects on ES after CSF ($F(1,15) = 140.81$; $p < 0.05$) (See Figure 3).

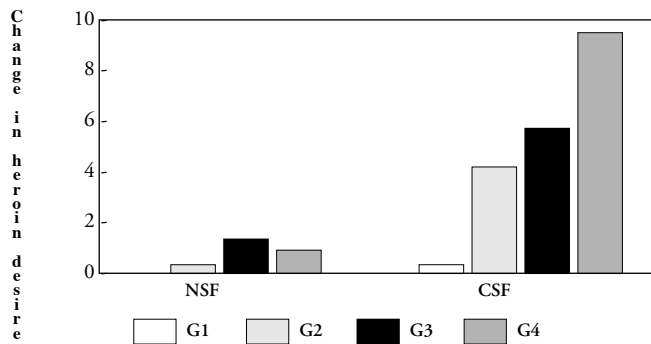


Figure 3: Effect of electric shock administered after the neutral stimuli film (NSF) and after context stimuli film (CSF) on heroin desire response change (0-10) in non-addict subjects (G1), in sporadic consumers (G2), in non-detoxified addict subjects (G3), and in detoxified addicts (G4).

Withdrawal symptoms self-perception (WSS)

4 (x2) ANOVA results showed statistically significant effects of Group ($F(3,60) = 283.14$; $p < 0.05$) and Stimulus ($F(1,60) = 565.15$; $p < 0.01$) factors, as well as their interaction ($F(3,60) = 359.14$; $p < 0.01$). Subjects in G4 showed significantly greater WSS change values on ES after CSF than after NSF ($F(1,15) = 892.38$; $p < 0.01$), and the same occurred in G3 subjects ($F(1,15) = 125.71$; $p < 0.01$). However, in G2 subjects the opposite effect was found, that is, significantly lower WSS change values on ES after CSF compared to those after NSF ($F(1,15) = 27.29$; $p < 0.01$). As far as G1 is concerned, no significant differences were observed between responses to ES after NSF and CSF. When comparing the four groups in ES after CSF condition, significantly greater WSS change values were observed in G4 than G3 ($F(1,30) = 299.06$; $p < 0.05$), than in G2 ($F(1,30) = 929.88$; $p < 0.05$) and than in G1 subjects ($F(1,30) = 808.33$; $p < 0.05$). Also, subjects in G3 showed significantly higher response change values on ES after CSF than G2 subjects ($F(1,30) = 196.40$; $p < 0.05$) or G1 subjects ($F(1,30) = 112.24$; $p < 0.05$). However, when comparing G2 subjects with those from G1, significantly lower response change values were shown by G2 than G1 on ES after CSF ($F(1,30) = 28.26$; $p < 0.05$) (See Figure 4).

Self-Perception Of Symptoms Mimetic To Those Caused By Heroin Effects (SMS)

4 (x2) ANOVA results showed statistically significant effects of Group ($F(3,60) = 214.28$; $p < 0.05$) and Stimulus ($F(1,60) = 75.39$; $p < 0.01$) factors, as well as their interaction ($F(3,60) = 215.22$; $p < 0.01$). Significant differences of response change on ES after NSF and CSF were found among G1, G2 and G3 groups, but not for G4, with response change values on ES after CSF

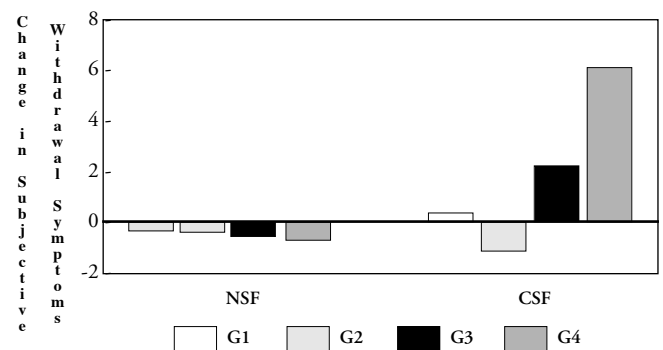


Figure 4: Effect of electric shock administered after the neutral stimuli film (NSF) and after context stimuli film (CSF) on subjective withdrawal response change (0-10) in non-addict subjects (G1), in sporadic consumers (G2), in non-detoxified addict subjects (G3), and in detoxified addicts (G4).

being significantly lower for G1 ($F(1.15)= 56.71$; $p<0.01$) and G3 ($F(1.15)= 305.41$; $p<0.01$) compared to the values obtained in ES after NSF. However, G2 subjects showed significantly greater change values on ES after CSF than after NSF ($F(1.15)= 75.31$; $p<0.01$). In addition, significant differences among the four groups were found on ES after CSF. That is, subjects in G4 showed significantly higher response change values than G3 subjects ($F(1.30)= 344.83$; $p<0.05$) and G1 subjects ($F(1.30)= 96.04$; $p<0.05$), but significantly lower values than G2 subjects ($F(1.30)= 68.16$; $p<0.05$). Similarly, G3 subjects showed lower response change values compared to those shown by G2 ($F(1.30)= 354.43$; $p<0.05$) and G1 ($F(1.30)= 241.24$; $p<0.05$) on ES after CSF. However, subjects from G2 showed greater response changes than G1 subjects ($F(1.30)= 113.30$; $p<0.05$) (See Figure 5).

DISCUSSION

Results in this study indicated that subjects detoxified from heroin emitted higher HR, EA, HD and WSS responses on ES after presentation of stimuli belonging to heroin consumption context than on ES presented after neutral stimuli or after heroin CSs presented to non-addict subjects, sporadic heroin consumers and non-detoxified subjects. These results may show that certain hyperalgesic CRs opposed to the analgesic unconditioned effects of heroin could form part of the behavioural repertoire of detoxified addict subjects. That is, these subjects, after being exposed to CSs belonging to the heroin consumption context might suffer a conditioned decrease of endogenous opiate levels and, hence, be more sensitive to noxious CS stimulation, which may facilitate a physiologically generalised activation state

with symptoms similar to those arising in the heroin withdrawal syndrome, and which -since it is self-perceived by the subject- might trigger high drug desire responses due to the action of a negative reinforcement mechanism (Trujillo, De la Fuente and Vila, 1995).

Results also indicated that detoxified subjects emitted mimetic responses to the effects of heroin on ES administered after context stimuli which are similar in intensity to those emitted on ES after neutral stimuli. Such a result may be considered logical if one bears in mind that that these kinds of subject, since they are not disaccustomed to CSs and, hence, are in a generalised activation state, did not succeed in self-perceiving relaxation states similar to those directly induced by heroin.

With regard to non-detoxified subjects, higher HR, EA, HD and WSS responses on ES administered in the presence of context stimuli than neutral stimuli, or administered after context stimuli to non-addict or sporadic consumers were observed. However, such responses were lower in intensity than those emitted by detoxified subjects. It was also observed that non-detoxified subjects produced lower SMS effects response change values on context stimuli than non-addict subjects, sporadic consumers and detoxified addicts, and than those emitted on ES after presentation of neutral stimuli. These results may be explained by the fact that, although non-detoxified subjects could show, under the control of heroin CSs, compensatory anticipatory CRs to drug effects, given that their levels of exogenous opiates in blood were high at the moment of assessment, such compensatory CRs could be counteracting the direct effects of such drug levels. Thus, these subjects being under the effects of heroin, CRs opposed to its effects could be competing with its neurochemical action, thereby causing conditioned withdrawal effects, although somewhat attenuated. In turn, this effect could serve as evidence supporting the environmental specificity of tolerance model and/or the environmental specificity of withdrawal states model.

As regards sporadic heroin consumers, it was observed that they produced lower HR, EA and WSS responses on ES after context stimuli than non-addicts or on ES without previous context stimuli. One could think that these subjects may come to produce anticipatory CRs on CSs belonging to the consumption context, at least for the three response systems mentioned, which are mimetic to responses unconditionally evoked by heroin when exerting analgesic and tranquillising effects at the physiological level. That is, if ES by itself, as a noxious stimulus,

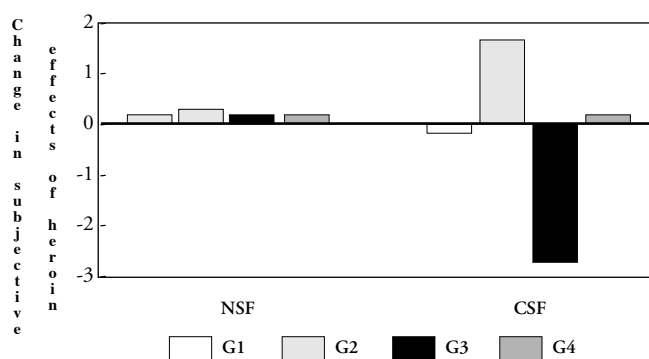


Figure 5: Effect of electric shock administered after the neutral stimuli film (NSF) and after context stimuli film (CSF) on change of subjective response similar to effects of heroin (0-10) in non-addict subjects (G1), in sporadic consumers (G2), in non-detoxified addict subjects (G3), and in detoxified addicts (G4).

causes increments in HR, EA and WSS and, however, when administered after CS lower values were obtained in these variables, it may be possible that what really happened was that CSs, when evoking CRs mimetic to the subjective and analgesic effects of heroin, were somehow counteracting hyperalgesic and activation effects induced by the ES. Some evidence in favour of this argument could be the results obtained by these subjects in SMS. Sporadic heroin consumers produced, on ES after context stimuli, a higher SMS response than on the same ES administered to non-addict subjects, non-detoxified subjects and detoxified addict subjects, or than on ES administered after neutral stimuli. It may be that context stimuli induced organic equilibrium conditioned states ("well-being"), and that these were self-perceived by this type of subject. However, an unexpected result was that these subjects produced higher HD responses on ES after context stimuli than those emitted on the same ES by non-addict subjects and detoxified subjects, or when administered after neutral stimuli, when one would expect -according to what has previously been posed- that they would be lower. However, this result could be due to the fact that context stimuli could have acted as consequent reward discriminative stimuli, hence triggering certain HD responses and, at the same time, evoking CRs mimetic to heroin effects in these subjects.

Overall, one may think that CRs opposed to heroin effects produced by detoxified subjects in the face of the context stimuli used were due to the establishment in their addictive past of a strong association between these stimuli and the withdrawal states they experienced. Hence, such CRs could be considered as empirical evidence in favour of conditioned withdrawal. In turn, following the same line of reasoning, it could also be explained that non-detoxified subjects produced CRs opposed to those induced by opiates, even when under the drug's effects at the time of assessment. These results may show that certain hyperalgesic responses, opposed to unconditioned analgesic responses evoked by heroin, could form part of the addict subject's behavioural repertoire, even after being detoxified from the substance in question. Thus, the context stimuli sequence might favour the conditioned depletion of the subject's endogenous opiates system (Arnold, Robinson, Spear and Snoterman, 1993; Illich, Salinas and Grau, 1991; Krank, 1987; Maier, 1989; Matzel and Miller, 1989; Ross, 1985), and hence make the subject more sensitive to contingent noxious stimulation which, in

turn, facilitates a generalised activation state at the physiological level with symptoms similar to those arising in the heroin withdrawal syndrome. These results may serve to corroborate in humans the results obtained with animals on the detection of hyperalgesic CRs evoked by environmental stimuli associated to organic states as a consequence of an abrupt removal of morphine (among others, Falls and Kelsey, 1989; Krank, 1987; Krank, Hinson and Siegel, 1981; McRae and Siegel, 1987; Ross, 1985; Sherman, Strub and Lewis, 1984).

It may be that context stimuli -when evoking conditioned responses of physiological imbalance (CRs compensatory to heroin effects)- were favouring the development of interoceptive stimuli and that, since these are self-perceived by the subject, were interpreted as withdrawal signs or symptoms capable, in turn, of eliciting responses of desire for heroin. That is, these withdrawal signs and symptoms might acquire the functionality of discriminative stimuli and, at least partially, make probable responses of private heroin desire and, perhaps, of explicit search and consumption, leading in turn to responses of a relapse into drug abuse under the control of a negative reinforcement mechanism. However, it would be simplistic to argue that a detoxified addict desires heroin and relapses into its use only because there is an underlying negative reinforcement mechanism at the behavioural level, since it is known that in every behavioural addictive process there are, in addition, positive reinforcement mechanisms that mediate, and which are maintained by the drug's rewarding effect. Moreover, other relevant factors may mediate, such as response cost factors for change of behavioural pattern (Nureya, 1985), factors related to decision taking under ambiguous stimulation (De la Fuente, Trujillo, Ortega, Martín and Estarellas, 1993), learning factors for interoceptive stimulation self-perception (Lubinsky and Thompson, 1989), etc.

With regard to the direction of responses for subjects sporadically consuming heroin, the fact that they produced CRs mimetic to analgesic and subjective effects unconditionally induced by the drug may be explained, given that, in their incipient addictive history, such context stimuli had been mainly associated with organic and subjective states induced by the drug's direct effects. That is, in states of equilibrium and, hence, of generalised sedation. And, probably, this is due to the fact that they have scarcely had withdrawal states, since they are in an addictive stage in which a significant tolerance to the opiate has not yet been developed. However, it is

important to emphasise that, in these subjects, mimetic CRs produced in addition to unconditioned effect of heroin may result in a greater central depression of the nervous system than that which is caused only by the pharmacological effect of heroin. Thus, the organism would be forced to homeostatically compensate such a depression in a quite active manner, which would favour a more efficient association among biological regulation responses and heroin stimuli. This may be accelerating the development of organic tolerance processes, and may explain the speed with which addictive behavioural chains are established. Support for the above is provided by the results obtained by Littleton and Little (1989). These researchers showed that repeated consumption of opiates in cell culture caused cellular compensatory effects which ended up normalising the concentration of activating nucleotides, as is the case of cyclic-monophosphatone-adenosin (AMP-c) and, hence, the cellular activation level; and that these regulatory adaptive effects may be due to an increased synthesis of adenil-ciclasa, hence compensating the inhibition produced by these substances. If we take into account this argument, it could be argued that after consumption of heroin there will always be homeostatic regulation effects and, hence, compensation of heroin's direct effects.

Some novel results obtained in this study which may lead to new empirical support for the phenomenon of environmental specificity of anticipatory responses to the effects of heroin were the following: (1) Detection of hyperalgesic CRs compensatory to the analgesic effects of heroin under the control of noxious stimulation after opiate context stimuli; (2) detection of subjective and analgesic CRs similar (mimetic) to those unconditionally evoked by heroin in the presence of noxious stimulation administered in the presence of this drug's CSs; (3) the detection of the addict's lack of need of expectations of drug's availability to produce anticipatory (mimetic and compensatory) CRs to the effects of heroin; (4) direction and intensity of anticipatory CRs of heroin effects probably depend on the addictive stage in which subjects are, and on whether or not these subjects are under the drug's effects; and (5) since we worked on this study with three groups of subjects with different addictive histories and with a control group, we believe it to have been shown that the detected anticipatory CRs were conditioned in origin (for a review on the topic, see Robbins and Ehrman, 1991), which allows us to refer to them as "conditioned responses", and not simply as "responses".

REFERENCES

- Arnold, H.M., Robinson, S.R., Spear, N.E. and Smotherman, W.P. (1993). Conditioned opioid activity in the rat fetus. *Behavioral Neuroscience*, *107*, 963-969.
- Childress, A.R., Hole, A.V., Ehrman, R.N., Robbins, S.J., McLelland, A.T. and O'Brien, C.P. (1993). Reactividad ante estímulos en la dependencia de la cocaína y los opiáceos: Visión general de las estrategias para afrontar los deseos irresistibles de droga y la excitación condicionada. In M.C. Casas y M. Gossop (comps.) *Tratamientos psicológicos en drogodependencias. Recaída y prevención de recaída* (pp.191-221). Sitges, Spain: Ediciones en Neurociencias.
- Childress, A.R., McLelland, A.T., Nalale, M. and O'Brien, C.P. (1987). Mood states can elicit conditioned withdrawal and craving in opiate abuse patients. *NIDA: Research Monograph Series*, *76*, 137- 144.
- Childress, A.R., McLelland, A.T. and O'Brien, C.P. (1986). Abstinence opiate abusers exhibit conditioned craving, conditioned withdrawal and reductions in both through extinction. *British Journal of Addiction*, *81*, 655-660.
- De la Fuente, E.I., Trujillo, H.M., Ortega, A.R., Martin, I. and Estarellles, R. (1993). Assessment in probability judgement: A model for combining sources. *The Statistician*, *42*, 561 -570.
- De Wit, H. and Stewart, S. (1981). Reinstatement of cocaine-reinforced responses in the rat. *Psychopharmacology*, *75*, 134- 143.
- Eikelboom, R. and Stewart, J. (1982). Conditioning of drug-induced physiological responses. *Psychological Review*, *89*, 507-528.
- Falls, W.A. and Kelsey, J.E. (1989). Procedures that produce context-specific tolerance to morphine in rats also produce context-specific withdrawal. *Behavioral Neuroscience*, *103*, 842-849.
- Grabowsqui, J. and O'Brien, C.B. (1981). Conditioning factors in opiate use. En N. Mello (comp.), *Advances in substance abuse*, Vol 2, (pp 69-121). Greenwich, C.T.: JAI.
- Hinson, R.E. and Siegel, S. (1983). Anticipatory hyperexcitability and tolerance to the narcotizing effect of morphine in the rat. *Behavioral Neuroscience*. *97*, 759-767
- Illich, P.A., Salinas, J.A. and Grau, J.W. (1991). Conditioned changes in pain reactivity: II. In search of the elusive phenomenon of conditioned hyperalgesia. *Behavioral Neuroscience*, *105*, 478-481.

- King, G.R., Joyner, C. and Ellinwood, E.H. (1994). Continuous or intermittent cocaine administration: Effects of amantadine treatment during withdrawal. *Pharmacology, Biochemistry and Behavior*, 47, 451-457.
- Krank, M.D. (1987). Conditioned hyperalgesia depends on the pain sensitivity measure. *Behavioral Neuroscience*, 101, 854-857.
- Krank, M.D., Hinson, R.E. and Siegel, S. (1981). Conditional hyperalgesia is elicited by environmental signals of morphine. *Behavioral and Neural Biology*, 32, 148-157.
- Lett, B.T. (1989). Repeated exposures intensify rather than diminish the rewarding effects of amphetamine, morphine, and cocaine. *Psychopharmacology*, 98, 357-362.
- Levine, D.G. (1974). "Needle Freaks": Compulsive self-injection by drugs users. *American Journal of Psychiatry*, 30, 37-42.
- Littleton, J.M. and Little, H.J. (1989). Adaptation in neural calcium channels as a common basis for physical dependence on central depressant drugs. In A.J. Goudie and M.W. Emmett Oglesby (Eds.), *Psychoactive drugs: Tolerance and sensitization*, (pp. 461-518). Clifton, New Jersey: The Humana Press Inc.
- Lubinski, D. and Thompson, T. (1987). An animal model of the interpersonal communication of interoceptive (private) states. *Journal of the Experimental Analysis of Behavior*, 48, 11-15.
- MacRae, J.R. and Siegel, S. (1987). Extinction of tolerance to the analgesic effect of morphine: Intracerebroventricular administration and effects of stress. *Behavioral Neuroscience*, 101, 790-796.
- Maier, S.F. (1989). Determinants of the nature of environmentally induced hypoalgesia. *Behavioral Neuroscience*, 103, 131 - 143.
- Matzel, L.D. and Miller, R.R. (1989). Development of shock-induced analgesia: A search for hyperalgesia. *Behavioral Neuroscience*, 103, 850-856.
- Nureya, A.M. (1985). Conducta de elección: La selectividad y el costo de cambio entre alternativas. *Revista de Análisis del Comportamiento*, 3, 27-35.
- Obál, F., Viesay, M.S. and Benedek, G. (1976). On the cybernetic system of the control of vegetative functions. *Recent Developments of Neurobiology in Hungary*, 5, 235-267.
- Pavlov, I.P. (1927). *Conditioned Reflex*. London: Oxford University Press.
- Robbins, S.J. and Ehrman, R. (1991, April). *Conditioned factors in alcoholism*. VA Merit Review.
- Ross, R.T. (1985). Blocking and unblocking of conditioned analgesia. *Learning and Motivation*, 16, 173-189.
- Schwarz-Stevens, K.S. and Cunningham, C.L. (1993). Pavlovian conditioning of heart rate and body temperature with morphine. Effects of CS duration. *Behavioral Neuroscience*, 107, 1039-1048.
- Sherman, J.E., Strub, H. and Lewis, J.W. (1984). Morphine analgesia: Enhancement by shock-associated cues. *Behavioral Neuroscience*, 98, 293-309.
- Siegel, S. (1985). Drug-anticipatory responses in animals. In L. White, B.
- Tursky and G.E. Schwartz (comps.), *Placebo: Theory, research and Mechanisms* (pp. 288-305). New York: The Guilford Press.
- Snyder, S.H. (1980). Los receptores de los opiáceos y sustancias opiáceas endógenas. In G. Pies et al. (eds), *El cerebro* (pp.164169). Barcelona: Labor, Investigación y Ciencia.
- Thompson, T. and Ostlund, W. (1965). Susceptibility to readdiction as a function of the addiction and withdrawal environments. *Journal of Comparative and Physiological Psychology*, 60, 388-392.
- Trujillo, H.M. (1992). *Análisis en humanos de respuestas condicionadas miméticas y compensatorias de los efectos de la heroína*. Doctoral thesis. Universidad de Granada. Granada.
- Trujillo, H.M. (1994). Tolerancia a las drogas y condicionamiento clásico. *Psicología Conductual*, 2, 43-69.
- Trujillo, H.M. (1995). Bases no farmacológicas del síndrome de retirada de la heroína: Un método para el análisis en humanos. *Psicología Conductual*, 3, 87-106.
- Trujillo, H.M. and De la Fuente E.I. (1994, March). *Methods of analysis for conditioned withdrawal to heroin effects*. Paper presented at First International Congress on Social Policy and Quality of Life. The European Union and Social Welfare, Granada, Spain.
- Trujillo, H.M., De la Fuente, E.I. and Vila, J. (1995). Hiperálgesia condicionada ante estímulos contextuales de la heroína: Especificidad temporal de la abstinencia. *Psicothema*, 7, 499-511.
- Wikler, A. (1948). Recent progress in research on the neurophysiological basis of morphine addiction. *American Journal of Psychiatry*, 105, 328-338.
- Wikler, A. (1973a). Dynamics of drug dependence. *Archives of General Psychiatry*, 28, 611- 616.
- Wikler, A. (1973b). Conditioning of successive adaptive responses to the initial effects of drug. *Conditional Reflex*, 8, 193-210.
- Wikler, A. (1980). *Opioid dependence: Mechanisms and treatment*. New York: Plenum Press.