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Evaluation of the central effects of alcohol and caffeine interaction

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1 The dynamic and kinetic interactions of alcohol and caffeine were studied in a double-blind, placebo controlled, cross-over trial. Treatments were administered to eight healthy subjects in four experimental sessions, leaving a 1 week wash-out period between each, as follows: 1) placebo, 2) alcohol (0.8 g kg^{-1}), 3) caffeine (400 mg) and 4) alcohol (0.8 g kg^{-1}) + caffeine (400 mg).

2 Evaluations were performed by means of: 1) objective measures: a) psychomotor performance (critical flicker fusion frequency, simple reaction time and tapping test), b) long latency visual evoked potentials ('pattern reversal'); 2) subjective self-rated scales (visual analogue scales and profile of mood states); 3) caffeine and alcohol plasma concentration determinations.

3 The battery of pharmacodynamic tests was conducted at baseline and at +0.5 h, +1.5 h, +2.5 h, +4 h and +6 h. An analysis of variance was applied to the results, accepting a $P < 0.05$ as significant. The plasma-time curves for caffeine and alcohol were analysed by means of model-independent methods.

4 Results obtained with caffeine in the objective measures demonstrated a decrease in simple reaction time and an increase in the amplitude of the evoked potentials; the subjects' self-ratings showed a tendency to be more active. Alcohol increased simple reaction time and decreased amplitude of the evoked potentials, although the subjects rated themselves as being active. The combination of alcohol + caffeine showed no significant difference from placebo in the objective tests; nevertheless, the subjective feeling of drunkenness remained. The area under the curve (AUC) for caffeine was significantly higher when administered with alcohol.

5 Only those objective tests which demonstrated a significant effect with caffeine were able to detect counteracting effects of caffeine over alcohol.

Keywords caffeine alcohol interaction psychophysiological measurements central nervous system

Introduction

According to a survey recently carried out in Spain, there are approximately one and a half million alcoholic men and half a million women, representing 7% of the total adult population and one of the most important health problems. In our country the costs produced by alcohol problems (health services, traffic and other accidents, and especially lost working time) amount to £5 × 10^9 yearly [1]. In our environment alcohol is frequently consumed in combination with caffeine. The effects on the central nervous system (CNS) of both substances have been extensively described, and it is known that caffeine alone has a generalized stimulant effect, decreasing sleepiness, fatigue and reaction time [2, 3], while alcohol induces a general psychomotor performance impairment [4].

The concomitant intake of alcohol and caffeine could produce counteracting effects on the CNS. Several studies have been conducted with contradictory results regarding this finding [5–11].

We designed a study with the following main aim: to evaluate the effects of alcohol as a depressant and caffeine as a stimulant on the CNS when administered

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alone or combined to healthy volunteers, using three different dynamic assessments; psychomotor performance tests, electrophysiological recordings (visual evoked potentials) and subjective feelings (self-rated scales). The time course of alcohol and caffeine plasma concentrations was also determined.

Methods

Subjects

Eight paid healthy male volunteers with a mean age of 24.5 years (range: 23–27), mean body weight of 71.6 kg (range: 62–80 kg) and a mean height of 176 cm (range: 171–185 cm) were included in the study. All showed normal findings in the physical and analytical examinations and none had a history of mental or neurological diseases. Only subjects who were considered moderate social alcohol drinkers were selected for the trial. None of the subjects took any medication during the experimental period, and they were requested to abstain from alcohol, coffee, tea or cola beverages 24 h before and throughout each experimental session. Subjects were fully informed about the nature and the potential risks of the study and gave their written consent to participate. The protocol was approved by the Local Ethics Committee of St Pau Hospital and was performed according to current ethical regulations for subjects undergoing biomedical research.

Treatments and experimental design

The trial was designed as an intra-individual comparison and placebo-controlled study. Treatments were administered randomly according to a cross-over, Latin square design in double-blind conditions keeping 1 week between each experimental session. They received single oral doses of the following treatments: 1) placebo (placebo-alcohol + placebo-caffeine); 2) alcohol (0.8 g kg^{-1}); 3) caffeine (caffeine 400 mg) 4) alcohol (0.8 g kg^{-1}) + caffeine (caffeine 400 mg);. All substances used in this study were prepared by the Department of Pharmacy of our hospital, caffeine or lactose being packed in identical hard gelatine capsules. The alcoholic drinks were served as a 400 ml orange juice solution using peppermint to mask the placebo drink and calculating alcohol content on an individual basis according to body weight. The drinks were then administered in three portions equally distributed over a drinking period of 30 min. The corresponding caffeine/placebo capsules were ingested at the beginning of the alcohol intake.

Subjects came to the four experimental sessions in couples and were tested individually. Each session started at 07.00 h with two basal evaluations of a battery of pharmacodynamic tests and continued at +0.5, +1.5, +2.5, +4 and +6 h post drug intake. Additionally, blood samples were drawn at baseline, +0.5, +1, +1.5, +2, +2.5, +3, +4 and +6 h in order to determine caffeine and alcohol plasma concentrations.

Test battery

Psychomotor performance

Critical flicker fusion (CFF) This test measures the level of cortical activity or arousal. The subject looks into a 45 cm long tube with a steady white background illumination. A red flickering light of 3 mm in diameter, centred on the bottom of the tube is continuously increased (fusion) or decreased (flicker) from 20 to 80 Hz at a speed of 1.5 Hz s^{-1}. The subject has to press a button when the light stops or starts flickering. In this way CFF is measured four times for both increasing and decreasing phases using the method of limits. The variable evaluated was the mean flicker-fusion frequency in Hz.

Simple reaction time (SRT) In this test visual stimuli, consisting in a 5 mm red light, are presented to the subject at varying intervals of 1 to 8 s selected randomly. A total of 30 stimuli is produced in a period of 2 min. The subject must respond to each stimulus as quickly as possible by pressing a button with the forefinger of the dominant hand. The variable for evaluation was the mean reaction time to the 30 visual stimuli in milliseconds.

Tapping test (TT) Reflex rate was measured by means of a tapping test. In a 6 × 6 cm metallic surface the subject has to hit as quickly as possible with a pen during 30 s. The variable for evaluation was the mean number of hits per second.

These three tests were performed using a microprocessor Multipsy 801 (BIODATA, Steinbach, Germany), which is routinely used in our Unit.

Neurophysiological measures

Long latency checkerboard pattern-reversal visual evoked potentials (VEPs) were recorded by means of a microcomputer Z-80 A Nicolet COMPACT FOUR, with the subjects comfortably sitting in a semi-reclining position in a special laboratory room with ambient light and noise. Luminance of the checkerboard was 10 cd/m^2 for the black fields and 290 cd/m^2 for the white fields. The visual size of the squares was 1 arc. The pattern was presented on a TV monitor together with a fixed central point using an ON-stimulation frequency of 0.9 Hz. Electroencephalographic (EEG) activity for VEP was recorded over occipital (Oz-Fpz) and central (Cz-A1) areas using Ag/AgCl electrodes (resistance was below 5 kΩ). Amplifier specifications were: upper frequency cut off 30 Hz; lower frequency cut off 1 Hz; sensitivity level 100 μV. The signal following each stimulus was digitalized at a rate of 1024 Hz for a period of 500 ms; resolution: 8 bits. To avoid artifacts on VEP waveforms, especially electro-oculogram (EOG) artifacts, the computer employed a voltage threshold detection criteria to identify and eliminate on-line any EEG epochs with amplitudes exceeding 95% of the sensitivity level established. At each recorded time, the digitalized signals were averaged in two consecutive non-overlapping blocks, each consisting of 50

sweeps free of artifacts. The latency and peak to peak amplitudes were scored by visual inspection and automatically calculated via a computer cursor program. Three peaks were identified in the waveform recorded over Oz-Fpz and three more in the waveform recorded over Cz-A1. The peaks were labelled as follows: N80, P100 and N130 for Oz-Fpz and N140, P200 and N270 for Cz-A1.

Subjective assessments

Visual analogue scales (VAS/100) To detect drug influence on subjective mood, a list with five 100 mm scales was used. Subjects had to mark the position on the scale, between two opposite mood states, which best reflected their present feeling. The five opposing pairs of words were: depressed/euphoric, active/passive, drunk/sober, nervous/calm and sleepy/awake.

Profile of mood states (POMS) A modified and shortened version of the original numerical scale [12] adapted by us to Spanish was used. It comprises 35 adjectives concerning subjective estimation of mood, which are to be rated by the subject from 0 (not at all) to 6 (extremely) according to their present situation. For interpretation purposes the various adjectives are grouped into five different mood dimensions: depression, activity, drunkenness, anxiety and drowsiness.

Alcohol and caffeine plasma concentrations

For plasma level determinations an indwelling catheter was inserted in an antecubital vein and kept patent throughout the study. At the times described above, 10 ml venous blood samples were collected in heparinized plastic tubes and immediately centrifuged to separate plasma which was then stored at −20° C until their posterior analysis. Plasma concentrations of alcohol and caffeine were assayed by immunofluorescence [13] and h.p.l.c. [14] methods, respectively. The inter-assay coefficients of variation were lower than 7%.

Clinical evaluations

An electrocardiogram (ECG) and biochemical and haematological analysis were performed before and at the end of each experimental session.

Systolic and diastolic blood pressure and heart rate in recumbent position were measured with an electronic device (DINAMAP, Critikon Inc., Tampa, Florida), at the same times at which the test battery was administered.

A list of 28 effects experienced as symptoms (EES), with four descriptive degrees of magnitude (none, mild, moderate and severe), containing the following items was also administered to the subjects: nausea, heartburn, diarrhoea, increased diuresis, blushing, cold feeling, warm feeling, lightheadedness, headache, buzzing noise, blurred vision, sparkling vision, mentally clumsy, euphoria, nervousness, susceptible, depressed, annoyed, talkative, tired, muscular cramps, clumsy motion, verbal incoordination, numbness of extremities, tachycardia, palpitations, dizziness and others.

Statistics

Pharmacodynamic data were evaluated by means of a multivariate analysis of variance (MANOVA) for repeated measures (one factor: drug) for each group of variables: psychomotor performance, latencies and amplitudes in VEPs and self-reported scales. Raw data was transformed as the extent of the effect over time (AUC_e) corrected by the individual basal values for objective behavioural and subjective variables, and considering grand averages of VEPs over post-drug times. The AUC_e was calculated applying the trapezoidal method as an overall index of pharmacodynamic response for each main variable.

Additional evaluations of the time-course of the effects were performed by means of ANOVAs (two factors: drug, time) for repeated measures applied to data expressed as differences from basal values.

The pharmacokinetic profile was defined by calculating the area under the concentration-time curve (AUC_c) from time zero to the last sample using the trapezoidal method. In addition, the peak plasma concentration (C_{max}) and the time required to achieve the latter (t_{max}) were determined directly from the experimental data [15]. Comparisons between each active treatment, alone and in combination, were assessed by means of Wilcoxon's test. ($SPSS^x$ Digital VAX 8800).

In all cases $P < 0.05$ was considered significant.

Results

Dynamics

No differences were found between the two basal values measured in the psychomotor performance tests at the beginning of each experimental session, so the average was computed and used when necessary in the subsequent calculations in order to get a more accurate estimate.

Objective behavioural, neurophysiological and subjective variables did not display any significant differences in the baseline assessments before each treatment, showing homogeneous baseline values in all the study days.

Psychomotor performance tests

The MANOVA applied to the psychomotor performance variables showed a significant treatment effect (Hotelling's t: 1.79, $P = 0.036$). Univariate F-tests only revealed significant differences in SRT ($F = 6.43$, $P = 0.005$) (Table 1).

Alcohol clearly increased SRT, while caffeine showed the opposite effect. Alcohol + caffeine and placebo had a similar profile and no significant differences were found between them (Figure 1). When analyzing

Table 1 Statistical significances after applying one factor (drug: four levels) MANOVAs for repeated measures to each group of variables with subsequent univariate *F*-tests

	Psychomotor performance	*Evoked potentials*		*Subjective assessments*	
		Latencies	*Amplitudes*	*VAS*	*POMS*
Hotellings	$P = 0.036$	$P = 0.297$	$P = 0.019$	$P = 0.017$	$P = 0.005$
		Occipital	*Occipital*		
Univariate	CFF = 0.822	N80 = 0.066	N80-P100 = 0.703	Depr. = 0.076	0.097
F-tests	SRT = 0.005	P100 = 0.410	P100-N140 = 0.858	Acti. = 0.516	0.375
significance	TT = 0.979	N140 = 0.483		Drun. = 0.028	0.007
		Central	*Central*	Anxi. = 0.198	0.548
		N140 = 0.055	N140-P200 = 0.015	Drow. = 0.251	0.208
		P200 = 0.100	P200-N270 = 0.008		
		N270 = 0.353			

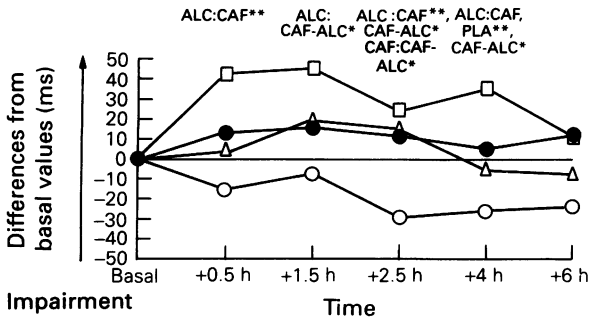

Figure 1 Time course of mean values in SRT expressed as differences from basal values ($n = 8$). CAF (○): caffeine 400 mg, ALC (□): alcohol 0.8 mg kg^{-1}, CAF-ALC (●): caffeine 400 mg + alcohol 0.8 mg kg^{-1}, PLA (△): placebo. X:X paired samples *t*-test, $^{**}P < 0.01$, $^{*}P < 0.05$. Alcohol significantly impaired simple reaction time, caffeine showed the opposite effect and caffeine + alcohol had a similar profile to placebo.

the time-course of the effects, the impairment produced after alcohol intake was statistically significant when compared with caffeine at 0.5, 2.5 and 4 h, compared with alcohol + caffeine at 1.5, 2.5 and 4 h, and with placebo at 4 h. In addition, the improvement seen after caffeine was statistically significant when compared with the interaction at 2.5 h.

There were no statistically-significant differences among treatments in either TT or CFF, though the AUC_e for CFF tended to show an increase in mean frequency with caffeine, and a decrease with alcohol; alcohol + caffeine and placebo were similar.

Visual evoked potentials

Two derivations of VEP were recorded, occipital and central. Three peaks were identified in each one: N80, P100 and N130 for the occipital derivation and N140, P200 and N270 for the central. Latencies and amplitudes of the identified peaks were analyzed.

The MANOVA applied to VEP latencies obtained from the grand averages over post-drug times showed no significant differences, while applied to VEP amplitudes it showed a significant treatment effect (Hotelling's *t*: 2.81, $P = 0.019$). Univariate *F*-tests only revealed significant differences in interpeak amplitudes measured at the central derivation (N140-P200: $F = 4.83$, $P = 0.015$; P200-N270: $F = 5.66$, $P = 0.008$) (Table 1).

Alcohol produced a significant decrease in both central interpeak amplitudes and caffeine a significant increase, while the interaction and placebo lay in-between (Figure 2). When analyzing the time-course of the effects, the decrease produced by alcohol intake was statistically significant when compared with caffeine at 0.5, 1.5 and 4 h in the N140–P200 amplitude, and at 0.5, 1.5 and 2.5 h in the P200-N270 amplitude. In addition, caffeine produced a statistically significant increase when compared with the interaction at 4 and 6 h in the N140-P200 amplitude, and at 2.5 h in the P200-N270 amplitude.

Subjective assessments

The MANOVA applied to subjective VAS assessments as AUC_e showed significant differences (Hotelling's *t*: 15.32, $P = 0.017$). The same occurred when a MANOVA was applied to subjective POMS assessments (Hotelling's *t*: 4.67, $P = 0.005$). Univariate *F*-tests only revealed significant differences in the scales measuring drunkenness (VAS: $F = 4.01$, $P = 0.028$; POMS: $F = 5.85$, $P = 0.007$) (Table 1).

Alcohol and alcohol + caffeine produced a significant feeling of drunkenness, both evaluated by VAS and POMS, which was not observed after caffeine or placebo. When analyzing the time-course of the effects it was observed that the significant feeling of drunkenness induced by alcohol and the interaction was statistically different from caffeine at 0.5, 1.5 and 2.5 h; in addition, the interaction was statistically different from placebo at 2.5 and from caffeine at 4 h when assessing subjective feelings with VAS (Figure 3). Alcohol and alcohol + caffeine were statistically different from caffeine at 0.5, 1.5 and 2.5 h and from placebo at 0.5 h; in addition, alcohol was statistically different from placebo at 2.5 and caffeine at 4 and 6 h when assessing feelings with POMS.

Furthermore, when analyzing the time-course of the effects, statistically significant differences in activity evaluated with both VAS and POMS were

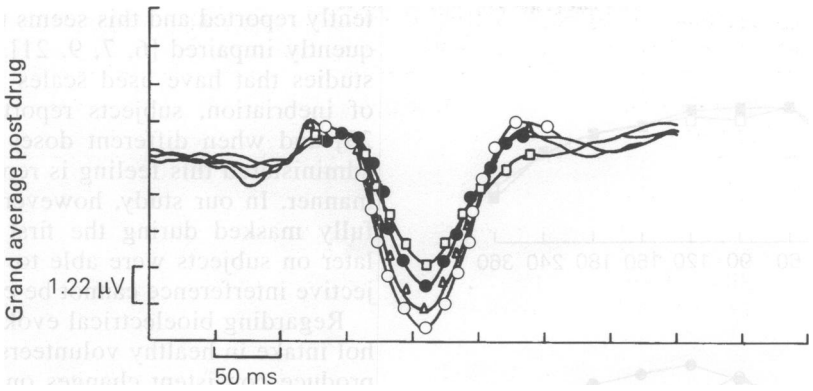

Figure 2 Long latency visual evoked potentials (pattern reversal) obtained in Cz-A1. Grand average after drug intake (16.000 responses: eight subjects, five times post-drug). Caffeine (○): caffeine 400 mg, ALC (□): alcohol 0.8 mg kg^{-1}, CAF-ALC (●): caffeine 400 mg + alcohol 0.8 mg kg^{-1}, PLA (△): placebo. Alcohol produced a significant decrease in both interpeak amplitudes and caffeine a significant increase, alcohol + caffeine and placebo lying in between.

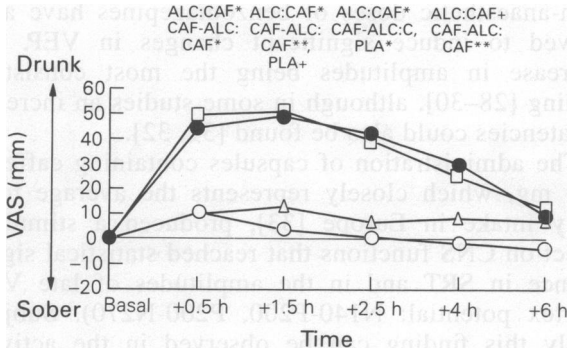

Figure 3 Time course of mean values in subjective mood related to drunkenness evaluated by VAS/100 expressed as differences from basal values (n = 8). CAF (○): caffeine 400 mg, ALC (□): alcohol 0.8 mg kg^{-1}, CAF-ALC (●): caffeine 400 mg + alcohol 0.8 mg kg^{-1}, PLA (△): placebo. X:X paired samples t-test, $^{**}P < 0.01$, $^{*}P < 0.05$, $^{+}P < 0.10$. Alcohol and alcohol + caffeine produced a significant feeling of drunkenness which was not observed after caffeine or placebo.

shown. Activity evaluated with VAS (active-passive) demonstrated a significant time effect (P = 0.026) in the two-way repeated measures ANOVA (drug, time) showing changes from pre-treatment values. Alcohol induced the highest increase in activity, being statistically different from caffeine and placebo only at 0.5 h. Activity evaluated with a numerical questionnaire (POMS) showed a significant drug by time interaction (P = 0.046) in the two-way repeated measures ANOVA (drug, time) showing changes from pre-treatment values. Alcohol produced a significant increase in activity at 0.5 h in comparison with placebo and a decreased at 2.5 h in comparison with caffeine.

None of the treatments studied affected statistically the subjective feelings of depression, anxiety or drowsiness.

Pharmacokinetics

Mean plasma concentration-time course of caffeine and alcohol after single oral administration of both compounds, separately or in combination, are plotted in Figure 4.

The AUC for alcohol when administered alone or combined with caffeine showed no statistical differences between the two conditions (alcohol: 5069.65 ± 736.8 mmol l^{-1} min; alcohol + caffeine: 5152.20 ± 1308 mmol l^{-1} min). However, the AUC for caffeine was significantly greater when combined with alcohol than when taken alone (caffeine: 2040.18 ± 512.27 μg ml^{-1} min; caffeine + alcohol: 2645.63 ± 567.8 μg ml^{-1} min; Wilcoxon P = 0.027).

Alcohol and caffeine bioavailability rates did not show any significant differences when taken alone or in combination, either in C_{max} (alcohol: 20.97 ± 1.78 mmol l^{-1}; alcohol + caffeine: 21.48 ± 4.22 mmol l^{-1}; caffeine: 9.10 ± 2.01 μg ml^{-1}; caffeine + alcohol: 9.83 ± 1.9 μg ml^{-1}) or in t_{max} (alcohol: 75 ± 25.1 min; alcohol + caffeine: 75 ± 16.43 min; caffeine: 95 ± 29 min; caffeine + alcohol: 120 ± 36.9 min).

Clinical evaluations

No changes were found either in the ECG, biochemical or haematological parameters. Systolic and diastolic blood pressure and heart rate were within the normal range throughout the study.

In the EES evaluations, alcohol (134 reports) produced the highest score followed by the interaction (124 reports), caffeine (66 reports) and finally placebo (50 reports). The symptoms and signs most frequently reported after caffeine were: euphoria (8.3%) and increased diuresis (7.8%). After alcohol these were: lightheadedness (8.9%), increased diuresis (8.9%) and feeling tired (8.2%). The latter items (increased diuresis and tired) were reported with a similar frequency (9.4%) after the alcohol + caffeine combination. Euphoria and lightheadedness were reported in 8% of occasions after alcohol + caffeine intake.

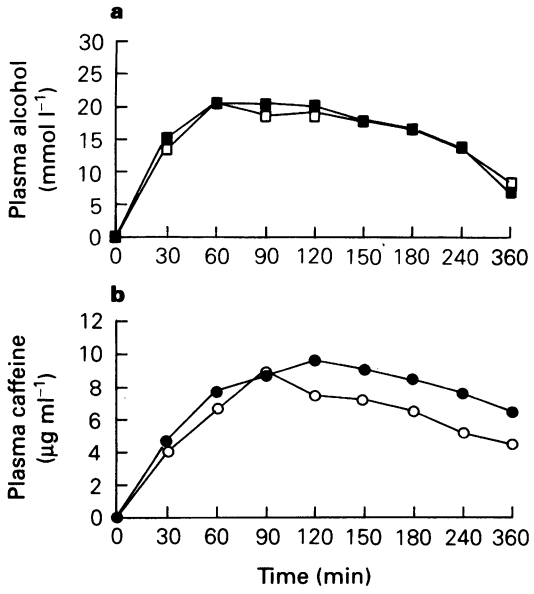

Figure 4 Mean alcohol (a) and caffeine (b) plasma concentrations after single oral doses either alone (open symbols) or in combination (closed symbols) (n = 8). CAF: caffeine 400 mg, ALC: alcohol 0.8 mg kg^{-1}, CAF-ALC: caffeine 400 mg + alcohol 0.8 mg kg^{-1}. AUC_c for alcohol showed no statistical differences between alcohol and caffeine + alcohol. AUC_c for caffeine was significantly greater after caffeine + alcohol than after caffeine.

Discussion

This double-blind, cross-over, placebo-controlled study after single oral doses of alcohol 0.8 mg kg^{-1}, caffeine 400 mg and the combination of both showed clearly different pharmacodynamic profiles after each compound taken separately, and relevant interactions when they were taken simultaneously.

Alcohol dosing adjusted to body weight (0.8 g kg^{-1}) administered to the healthy volunteers was chosen to produce blood alcohol concentrations near to the upper limit considered legally permissible for driving in our country, that is 17.4 mmol l^{-1}. In fact, mean blood alcohol concentration ranged from 13.5 mmol l^{-1} to 20.4 mmol l^{-1} between 30 and 240 min. This acute alcohol intake produced depressant effects on CNS function that reached statistical significance in the increase of SRT and in the amplitude decrease of late VEP (vertex potential: N140-P200, P200-N270). No significant effects could be observed in CFF and TT nor in the latencies of late VEP. As could be expected, the volunteers self-rated themselves drunk throughout the experimental session, more active during the first hours and progressively becoming clearly passive.

These results are in agreement with previous experimental data reported in several studies. The administration of alcohol doses ranging from 0.5 mg kg^{-1} to 1.5 mg kg^{-1} causes impairment of cognitive and psychomotor performance tasks [6, 7, 9–11, 16–21]. Marked increases in SRT have been consistently reported and this seems to be the task most frequently impaired [6, 7, 9, 21]. Subjectively, in those studies that have used scales to measure the degree of inebriation, subjects reported feeling drunk [22, 23] and when different doses of alcohol have been administered this feeling is reported in a dose related manner. In our study, however, alcohol was successfully masked during the first part of its ingestion, later on subjects were able to differentiate, so a subjective interference cannot be completely ruled out.

Regarding bioelectrical evoked activity, acute alcohol intake in healthy volunteers has been described to produce consistent changes on auditory EP, reducing amplitudes but not affecting latencies [24, 25]. After different alcohol doses (0.41, 0.82, 1.23 mg kg^{-1}) somatosensory EP and VEP were recorded, the highest dose inducing a reduction in amplitudes without latency changes when compared with placebo [26]. Other CNS depressant substances produce similar changes on EP, e.g after 330 mg day^{-1} of propranolol, decreases in VEP amplitudes could be observed [27]. Non-anaesthetic doses of benzodiazepines have also proved to induce significant changes in VEP, the decrease in amplitudes being the most consistent finding [28–30], although in some studies an increase in latencies could also be found [31, 32].

The administration of capsules containing caffeine 400 mg, which closely represents the average total daily intake in Europe [33], produced a stimulant effect on CNS functions that reached statistical significance in SRT and in the amplitudes of late VEP (vertex potential: N140-P200, P200-N270). Subjectively this finding can be observed in the activity scale. Although subjects remained free of caffeine intake for 24 h, these results can hardly be explained by relief of caffeine withdrawal as they were not heavy caffeine consumers.

Improvements in cognitive and objective performance measures have been found by Franks *et al.* [6], Moskowitz & Burns [8], Nash [9] and Clubley *et al.* [34] when doses from 75 to 450 mg caffeine were administered. Conversely no such effects have been described when caffeine 150 to 500 mg was administered [10–11]. Subjective findings of caffeine effects are mainly the induction of alertness and reduction of calmness. This was reported by Rapaport *et al.* [2] with caffeine administered to children and adults, and by Nuotto *et al.* [10] in healthy young volunteers.

Some stimulant substances such as nicotine [35] or amphetamine [36] have respectively shown increases in auditory and visual amplitudes of EP, which is in accordance with the increases in VEP amplitudes observed in the present study with caffeine. However, the EP pattern of psychostimulant substances remains unclear. Another usual finding with this type of drugs is a decrease in latencies. These different patterns of effects could be largely explained by the different chemical structures of stimulant compounds [37].

When alcohol 0.8 mg kg^{-1} and caffeine 400 mg were administered together, our findings in the objective assessments suggest an antagonistic effect. In all variables studied, both placebo and the combination

lay somewhere between alcohol and caffeine alone, reaching statistical significance when the assessments were able to discern caffeine effects clearly, i.e. SRT and in the amplitudes of central derivations of VEP. Subjectively this antagonistic effect was not observed, the perception of drunkenness by the subjects being similar after alcohol alone and when combined with caffeine.

The studies conducted to date have shown contradictory results, demonstrating only in some cases an antagonistic interaction. Caffeine 300 mg counteracts the impairment on cognitive tasks and motor functions produced by 0.75 mg kg^{-1} of alcohol [6]. On the contrary, Osborne & Rogers [11], found that 150 mg caffeine and 0.8 mg kg^{-1} alcohol produced the greatest impairment in reaction time when administered together. Results in both directions were found with caffeine 500 mg and 0.5 mg kg^{-1} alcohol, which antagonized colour differentiation and arithmetic procedures but not verbal responses [5]. Nuotto *et al.* [10], concluded that caffeine did not clearly counteract alcohol effects in subjective and objective measures after performing two experimental designs with 20 healthy volunteers, using 200 and 500 mg caffeine and 1.0 g kg^{-1} alcohol in the first and 250 mg caffeine and 0.7 and 1.5 g kg^{-1} alcohol in the second. Finally, Keuchel *et al.* [7], using the combination of 0.3 mg kg^{-1} alcohol and 300 mg caffeine described inter-sex differences, synergistic in men and antagonistic in women. When caffeine interaction was evaluated using other CNS depressant drugs like benzodiazepines or barbiturates [38, 39], similar inconsistent results were obtained. Subjectively the principal effect produced by alcohol, drunkenness, is not reversed by caffeine. In this sense our results are in accordance with the subjective results obtained by Nuotto *et al.* [10].

Up to date there are no studies reflecting alcohol + caffeine interaction effects on EP or other electrophysiological measurements, so, there are no previous data to compare the finding that caffeine is able to counteract the effect of alcohol on VEP.

Kinetic results obtained in this study are in accordance with previously published data [40] which demonstrated that alcohol, in commonly consumed acute amounts, is a strong inhibitor of caffeine metabolism. The pharmacodynamic findings cannot be explained by kinetic mechanisms as alcohol plasma concentrations were the same after both ingestions, while after caffeine the AUC_c was greater when combined with alcohol, though caffeine did not display greater dynamic effects.

No changes were found in any of the clinical safety parameters evaluated. In the EES evaluations the most frequent symptoms and signs after caffeine and alcohol were reported with a similar frequency after alcohol + caffeine combination suggesting that the interaction did not reverse these symptoms.

The controversial dynamic results of the interaction of alcohol and caffeine presently available, are probably due to the diversity in doses and methods employed for its assessment. Therefore, it may be concluded that after an acute administration to healthy young volunteers in our experimental conditions, caffeine and alcohol when administered separately display their well-known behavioural central effects as a psychostimulant and depressant, respectively. The objective assessments which showed the clearest antagonistic effects were those able to detect caffeine effects, i.e only those tests able to detect an enhancement due to a CNS stimulant showed an antagonistic interaction between treatments. In our experimental conditions, the most sensitive tests to measure enhancement and the interaction of drug effects were SRT followed by VEP and CFF. Nevertheless, questions remain as to whether higher doses of caffeine would reverse alcohol effects on other psychomotor performance tests and whether these objective effects would be accompanied by a full reversal of subjective feelings.

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