

# Comparison Between Subjective Feelings to Alcohol and Nitrogen Narcosis: A Pilot Study

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Received 7 June 1995; Accepted 14 June 1995

MONTEIRO, M. G., W. HERNANDEZ, N. B. FIGLIE, E. TAKAHASHI AND M. KORUKIAN. *Comparison between subjective feelings to alcohol and nitrogen narcosis: A pilot study.* ALCOHOL 13(1) 75-78, 1996.—Nitrogen narcosis is often compared to alcohol intoxication, but no actual studies have been carried out in humans to test the comparability of these effects. If a common mechanism of action is responsible for the behavioral effects of these substances, biological variability of response to alcohol should correlate to that of nitrogen in the same individual. To test this hypothesis, subjective feelings were assessed in two separate occasions in 14 adult male, healthy volunteers, nonprofessional divers. In one occasion, each subject received 0.75 ml/kg (0.60 g/kg) alcohol 50% (v/v PO) and in another day underwent a simulated dive at 50 m for 30 min in a hyperbaric chamber. There was a significant correlation between reported feelings in the two sessions; subjects who felt less intoxicated after drinking also felt less nitrogen narcosis during the simulated dive. The results, although preliminary, raise the hypothesis that ethanol and nitrogen may share the same mechanisms of action in the brain and that biological differences might account for interindividual variability of responses to both ethanol and nitrogen.

Ethanol      Nitrogen narcosis      Genetic differences      Intoxication      Hyperbaric environment

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NITROGEN narcosis is often compared to alcohol intoxication in anecdotal reports, but no actual studies have been carried out in humans to test the comparability of these effects. Nitrogen is a biologically inert gas, and increased partial pressures of nitrogen lead to feelings of euphoria, high, light headedness, and motor incoordination that worsen as its concentration in the breathed air increases (4,18). A great interindividual variability is also reported in relation to nitrogen narcosis (4,5,10,17).

Depending on the dose, alcohol also produces excitatory effects, intoxication, incoordination, and relaxation. At higher doses, depressant effects predominate, which can lead to unconsciousness and even death (27). Several lines of evidence have indicated that ethanol-inducing mood, behavioral, and biochemical effects not only present wide interindividual differences but also seem to be regulated by genetic factors (6,7,9,22,25). In humans, for example, sons of alcoholics present less feelings of intoxication after taking three to five alcoholic standard drinks, and this less intensity of response has been related to an innate higher tolerance and to a higher vulnerability to develop alcohol dependence later in life (16,

22-24). However, the biological basis for this blunt response to alcohol has not yet been clarified.

It is plausible to hypothesize that if ethanol and nitrogen shared a common mechanism of action, less intense feelings of narcosis should be reported among individuals who report less reactions after drinking as well. To test this possibility, the present pilot study was undertaken.

## METHOD

Fourteen male, healthy volunteers, nonalcoholics, between 19-43 years of age, all certified divers, with no past histories of diving accidents or decompression sickness, were selected for the study. Selection was made through a structured clinical interview covering demographic information, medical and diving history, alcohol, tobacco, and drug use, personal and family history of alcohol- and drug-related problems, and other psychiatric disorders. All subjects who fulfilled diagnostic criteria for alcohol/drug abuse or dependence according to DSM III-R criteria (2) were excluded from the sample.

For the purpose of this study, a family history positive

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(FHP) was considered when a first-degree relative fulfilled DSM III-R criteria for alcohol dependence (sons of alcoholic mothers were also excluded because of the potential effects of alcohol on the fetus). When no history in either first- or second-degree relatives was reported the subject was considered as a family history negative (FHN). Each volunteer underwent a complete medical examination including an ECG and a comprehensive laboratory evaluation before entering the study.

All subjects answered a self-rated scale of expectations about their feelings during a simulative dive between 30–50 m and after drinking three to four drinks in 10 min. Each of the 12 expectancy feelings were the same used in the experimental sessions [Subjective High Assessment Scale (SHAS)] (22), and included positive (high, elated) and negative (uncomfortable, confused) aspects of intoxication.

Each subject voluntarily signed an informed consent form before entering the study. The protocol was approved by the Ethics Committee of Escola Paulista de Medicina.

#### General Protocol

Volunteers participated in a two-session protocol, on different days, in groups of four (minimum number of subjects required for an hyperbaric session). For eight subjects, the first session was the ethanol challenge whereas for the others it was the hyperbaric exposure (crossover design). For all volunteers, it was asked that 24 h before each session no alcohol or drugs were used. All sessions were carried out in the morning, and a padronized breakfast (orange juice and toast with butter) was given to them.

#### Ethanol Challenge Session

The ethanol session was carried out at the Clinical Psychobiology Research Center at Escola Paulista de Medicina in a temperature-controlled room in 1 ATA air (1 atmosphere absolute air). Volunteers were weighed upon arrival to the Centre, and after baseline measures of blood pressure, pulse, and blood alcohol levels, they received 0.75 ml/kg (or 0.6 g/kg) of body weight ethanol administered as a 50% (v/v) solution mixed with a sugar-free carbonated beverage and consumed during 10 min. They were asked to fill out a visual analog scale with 36 equal divisions (ranging from 0, not at all, to 36, extremely) for each of 12 items (uncomfortable, high, anxious, confused, elated, dizzy, sweating, nausea, light headiness, weak, tense, and difficulty concentrating) to self-rate their feelings after drinking (SHAS) (22). This was repeated every 30 min thereafter until 120 min postdrinking. Blood alcohol concentrations (BAC) were measured through a breath-analyzer, at baseline and every 30 min after ethanol administration.

#### Hyperbaric Chamber Session

In groups of four, volunteers underwent a simulative dive at 50 m (equivalent to 6 ATA air) for 30 min (initially 16 volunteers participated in the study but two were excluded from analyses afterwards due to incomplete data) in a hyperbaric chamber, breathing air. Before entering the chamber, at 50 m, and after the simulative dive, they self-rated their feelings of intoxication using the same visual analog scale described above (SHAS).

The dive profile was as follows: mean of 16 min for descent; mean bottom time 38 min; decompression time 1 : 58 min on air.

#### Statistical Analysis

Pearson's correlation coefficient was calculated for each item of the SHAS, using the maximum score from each session for each subject. A value of  $p \leq 0.05$  was considered statistically significant.

#### RESULTS

Table 1 shows the general characteristics of the subjects studied. Their mean age was  $28.5 \pm 7.2$  years, and they reported  $6.5 \pm 4.5$  years of diving experience after certification. Nine of them had never done a hyperbaric test before. Their alcohol consumption was moderate, averaging approximately 62 g of ethanol per week in the last 3 months.

There was no significant order effect in the crossover design. No significant correlations were found in their expectations about their feelings after drinking or during narcosis (data not shown).

The mean blood alcohol concentration at 30 min after the ethanol challenge was  $122.2 \pm 23.4$  mg/dl, and at 60 min it was  $96.6 \pm 27.8$  mg/dl. Table 2 shows the mean scores for each item of the SHAS during peak blood alcohol levels in the ethanol session and the mean scores for the same items at 50 m in the hyperbaric chamber. Overall, interindividual variability was found for most items in both sessions, whereas the intensity of reported feelings after the alcohol challenge was higher than those reported at 50 m. The same table shows the correlation coefficients found for each item of the SHAS. As can be seen, for most subjective feelings, a significant correlation was found, indicating that those with more intense reactions after drinking showed more intense reactions during nitrogen narcosis as well; those with less intense feelings in one session reported less intense reactions in the other.

On the other hand, reports of physical symptoms did not correlate due to the characteristics inherent to each situation: sweating is a feature always present in a simulative dive (temperature increases as pressure does) whereas it is uncommon during a drinking session in a temperature-controlled room. On the other hand, nausea may appear after drinking whereas this is not expected during a simulative dive.

Finally, to explore the relationship between feelings of intoxication and a family history of alcoholism, Table 3 shows the mean results separated by family history. Although statistical analysis was not carried out due to the small sample size of one of the groups (FHP  $N = 4$ ), a trend toward less intense feelings after drinking was seen for sons of alcoholics compared to sons of nonalcoholics. Apparently, sons of alcoholics reported the least intense feelings of narcosis during the simulative dive as well.

TABLE 1  
GENERAL CHARACTERISTICS OF  
14 MALE VOLUNTEERS

Characteristic	Mean $\pm$ SD
Age (years)	28.5 $\pm$ 7.2
Weight (kg)	76.2 $\pm$ 12.3
Height (cm)	176.8 $\pm$ 14.5
Diving experience	
Years of diving	6.5 $\pm$ 4.5
% Previous Hyperbaric Test	36%
Hours of dive	287 $\pm$ 267
Alcohol consumption (g/week)	61.97 $\pm$ 51.2

TABLE 2  
MEAN SCORES AT PEAK ALCOHOL LEVELS (ALCOHOL) AND AT 50 M  
IN THE HYPERBARIC CHAMBER (NITROGEN) FOR 14 VOLUNTEERS  
AND PEARSON'S CORRELATION COEFFICIENTS BETWEEN MAXIMUM  
SCORES GIVEN IN EACH SESSION ON EACH ITEM OF SHAS

SHAS Item	Alcohol	Nitrogen	<i>r</i>	<i>p</i>
Uncomfortable	2.1 ± 2.8	3.1 ± 3.81	-0.0293	0.460
High	11.7 ± 11	3.7 ± 4.42	0.6925	0.003
Anxious	3.0 ± 2.6	3.7 ± 4.19	0.5061	0.032
Confused	5.5 ± 6.2	1.9 ± 3.12	0.3912	0.083
Elated	13.4 ± 10.9	5.0 ± 8.19	-0.0060	0.492
Dizzy	11.0 ± 10.9	3.5 ± 5.27	0.0602	0.419
Sweating	1.6 ± 3.0	6.6 ± 7.49	0.1205	0.341
Nausea	1.2 ± 2.1	0.21 ± 0.58	0.2732	0.172
Light head	6.1 ± 6.6	1.2 ± 1.9	0.6255	0.008
Weak	2.3 ± 3.3	0.9 ± 2.4	0.1576	0.295
Tense	0.8 ± 1.8	0.8 ± 2.1	0.1178	0.344
Dif. concentrate	7.3 ± 6.4	2.6 ± 4.0	0.5249	0.027

## DISCUSSION

Although there is still little agreement about how and where ethanol and general anaesthetics act, a number of investigations have now indicated that binding to amphiphilic pockets or clefts on proteins can account for the relative anaesthetic potency of a diverse range of simple agents, including ethanol (13). One of the possible specific CNS targets for their primary effects is GABA<sub>A</sub> inhibitory receptors, which are potentiated by most anaesthetics and ethanol (12,13).

A number of investigations have initially indicated that alterations in membrane fluidity may be related to the biological effects of ethanol and other anaesthetics (3,8,19-21). These hypotheses have been refined to incorporate the direct involvement of proteins, and disturbances at the boundary lipids surrounding membrane proteins may be preferentially affected (13).

Neuronal membranes of mice genetically selected for high sensitivity to the hypnotic effects of ethanol are more "fluid"

after ethanol exposure, when compared with neuronal membranes of mice less sensitive to these same effects (14).

In addition, it has been shown that hyperbaric exposure directly antagonizes ethanol's and other anaesthetics' behavioral effects in laboratory animals (15,26). Increased pressure may block or counteract the acute effects of ethanol in critical microenvironments of brain cells or pressure may force ethanol out of its site of action (1,11).

Genetically determined differences in the response of intoxicated animals to the effects of pressure were also recently verified, thus increasing the evidences for the CNS membrane as ethanol's primary site of action (1). Because biological differences in membranes are under genetic control, interindividual differences in response to ethanol and nitrogen may be at least partly explained by the same mechanisms of action.

The present pilot study was the first attempt to compare in human subjects the acute effects of ethanol with those of nitrogen narcosis. There was no correlation between expectan-

TABLE 3  
COMPARISON BETWEEN FHPs AND FHNs ON MEAN ± SD MAXIMUM BLOOD  
ALCOHOL LEVELS (BAC), MAXIMUM SYMPTOMS OF INTOXICATION AFTER ALCOHOL,  
AND MAXIMUM SYMPTOMS AT 50 m

	Alcohol		Nitrogen	
	FHP (N = 4)	FHN (N = 10)	FHP (N = 4)	FHN (N = 10)
BAC (mg/dl)	120.7 ± 26.0	147.3 ± 30.5	—	—
SHAS items				
Uncomfortable	0.5 ± 0.6	2.8 ± 3.1	1.75 ± 2.4	3.6 ± 4.2
High	0.7 ± 0.9	16.1 ± 9.9	0	5.2 ± 4.4
Anxious	0.7 ± 0.9	3.9 ± 2.5	1.2 ± 1.5	4.7 ± 4.5
Confused	1.5 ± 3.0	7.1 ± 6.5	1.0 ± 2.0	2.3 ± 3.5
Elated	5.7 ± 5.2	16.5 ± 11.2	7.0 ± 14.0	4.2 ± 5.4
Dizzy	1.7 ± 1.7	14.7 ± 10.8	1.5 ± 3.0	4.3 ± 5.9
Sweating	0	2.2 ± 3.4	0.75 ± 0.96	9.0 ± 7.7
Nausea	0	1.7 ± 2.3	0	0.3 ± 0.7
Light Head	0.5 ± 1.0	8.4 ± 6.5	0.25 ± 0.5	1.6 ± 2.2
Weak	0.25 ± 0.5	3.1 ± 3.6	0	1.3 ± 2.8
Tense	0	1.2 ± 1.9	0	1.2 ± 1.9
Dif Conc.	1.5 ± 1.91	9.6 ± 6.0	1.5 ± 2.4	3.1 ± 4.6

cies before each session with the subjects' feelings of intoxication (data not shown), and therefore the results probably do not reflect expectation. However, it must be taken into consideration some caveats of the present study design. First, no placebo session was performed, and thus it could be argued that effects registered were due to alcohol or atmospheric exposure vs. environmental or group interactions in an unusual setting such as an hyperbaric chamber. Second, although measures of blood alcohol levels were compatible with intoxication, no other direct measure of intoxication was utilized. Third, subjects were tested in groups, adding another confounding variable in the determination of true pharmacological effects of treatment. Fourth, the environmental conditions where the sessions took place were different, thus making comparisons again difficult.

Finally, the trend found for a less intense response to alcohol and to nitrogen among sons of alcoholics was also coincident with findings from the literature (22–24), which may be

one more evidence that similar biological and genetic differences underline interindividual variability of response to both substances. At the same time, as no statistical analysis was performed to compare expectancies of sons of alcoholics with those of controls, it is possible that expectation could be a confounding variable, but this needs to be further investigated.

In conclusion, this pilot study indicates that alcohol and nitrogen may have a common site of action in the central nervous system, as has been suggested by animal studies (1, 11). This possibility should be further investigated.

#### ACKNOWLEDGEMENTS

Part of this work was presented at the Research Society on Alcoholism Annual Meeting, San Antonio, TX, June, 1993. Financial support from AFIP and FAPESP. The authors are grateful to Prof. Denise Botter, Prof. Monica Sandoval, and Patricia Viana for the statistical analyses of the data.

#### REFERENCES

- Alkana, R. L.; Finn, D. A.; Jones, B. L.; Kobayashi, L. S.; Babbini, M.; Bejanian, M.; Syapin, P. J. Genetically determined differences in the antagonistic effect of pressure on ethanol-induced loss of righting reflex in mice. *Alcohol. Clin. Exp. Res.* 16:17–22; 1992.
- American Psychiatric Association. Diagnostic and statistical manual, 3rd ed. revised. Washington, DC: American Psychiatric Press; 1987.
- Beaugé, F.; Stibler, H.; Borg, S. Abnormal fluidity and surface carbohydrate content of the erythrocyte membrane in alcoholic patients. *Alcohol. Clin. Exp. Res.* 9:322–326; 1985.
- Bennett, P. C. Inert gas narcosis In: Bennett, P.; Elliott, D., eds. *The physiology and medicine of diving*, 3rd ed. California: Best Publishing Co.; 1982:170–193.
- Brauer, R. W.; Beaver, R. W.; Hogue, C. D.; Ford, B.; Goldman, S. M.; Venters, R. T. Intra- and interspecies variability of vertebrate pressure neurological syndrome. *J. Appl. Physiol.* 37:844–851; 1974.
- Crabbe, J. C. Sensitivity to ethanol in inbred mice: Genotypic correlations among several behavioral responses. *Behav. Neurosci.* 2:280–289; 1983.
- Crabbe, J. C.; Kosobud, A.; Tam, B. R.; Young, E. R.; Deutsch, C. M. Genetic selection of mouse lines sensitive (COLD) and resistant (HOT) to acute ethanol hypothermia. *Alcohol Drug Res.* 7:163–174; 1987.
- de Fiebre, N. C.; Marley, R. J.; Wehner, J. M.; Collins, A. C. Lipid solubility of sedative-hypnotic drugs influences the hypothermic and hypnotic responses of long-sleep and short-sleep mice. *J. Pharmacol. Exp. Ther.* 263:232–240; 1992.
- Dudek, B. C.; Phillips, T. J. Distinctions among sedative disinhibitory and ataxic properties of ethanol in inbred and selectively bred mice. *Psychopharmacology (Berlin)* 101:93–99; 1990.
- Fothergill, D. M.; Hedges, D.; Morrison, J. B. Effects of CO<sub>2</sub> and N<sub>2</sub> partial pressure on cognitive and psychomotor performance. *Undersea Biomed. Res.* 18:1–19; 1991.
- Franks, N. P.; Lieb, W. R. Molecular mechanisms of general anaesthesia. *Nature* 300:487–493; 1982.
- Franks, N. P.; Lieb, W. R. Mechanisms of general anaesthesia. *Environ. Health Perspect* 87: 199–205; 1990.
- Franks, N. P.; Lieb, W. R. Molecular and cellular mechanisms of general anaesthesia. *Nature* 367:607–614; 1994.
- Goldstein, D. B.; Chin, J. H.; Lyon, R. C. Ethanol disordering of spin-labelled mouse brain membranes: Correlation with genetically determined ethanol sensitivity of mice. *Proc. Nat. Acad. Sci. USA* 70:4231–4233; 1982.
- Halsey, M. J.; Wardley-Smith, B. Pressure reversal of narcosis produced by anaesthetics, narcotics and tranquilizers. *Nature* 257:811–813; 1975.
- Hill, S. Y.; Steinhauer, S. R.; Zubin, J. Cardiac responsivity in individuals at high risk for alcoholism. *J. Stud. Alcohol* 53:378–388; 1992.
- Hunter, W. L.; Bennett, P. C. The causes, mechanisms and prevention of the high pressure nervous syndrome. *Undersea Biomed. J.* 1:1–28; 1974.
- Lippmann, J. *Deeper into diving*, 1st ed. Carnegie: J. P. Publications; 1990.
- Lyon, R. C.; McComb, J. A.; Schreurs, J.; Goldstein, D. B. A relationship between alcohol intoxication and the disordering of brain membranes by a series of short-chain alcohols. *J. Pharmacol. Exp. Ther.* 218:669–675; 1981.
- Marley, R. J.; Miner, L. L.; Wehner, J. M.; Collins, A. C. Differential effects of central nervous system depressants in long-sleep and short-sleep mice. *J. Pharmacol. Exp. Ther.* 238:1028–1033; 1986.
- Roth, S. H. Membrane and cellular actions of anaesthetic agents. *Fed. Proc.* 39:1595–1599; 1980.
- Schuckit, M. A. Subjective responses to alcohol in sons of alcoholics and control subjects. *Arch. Gen. Psychiatry* 41:879–884; 1984.
- Schuckit, M. A. Low level of response to alcohol as a predictor of future alcoholism. *Am. J. Psychiatry* 151:184–189; 1994.
- Schuckit, M. A.; Gold, E.; Risch, C. Serum prolactin levels in sons of alcoholics and controls. *Am. J. Psychiatry* 144:854–859; 1987.
- Smolen, A.; Smolen, T. N. Demonstration of a threshold concentration for ethanol at the time of regaining the righting response in long-sleep and short-sleep mice. *Alcohol Drug Res.* 7:279–283; 1987.
- Syapin, P. J.; Chen, J.; Finn, D. A.; Alkana, R. L. Antagonism of ethanol-induced depression of mouse locomotor activity by hyperbaric exposure. *Life Sci.* 43:2221–2229; 1988.
- Tabakoff, B.; Hoffmann, P. L.; Petersen, R. C. Advances in neurochemistry: A leading edge of alcohol research. *Alcohol Health Res. World* 14:138–143; 1990.