Pergamon

Alcohol, Vol. 12, No. 6, pp. 559–562, 1995
Copyright © 1995 Elsevier Science Inc.
Printed in the USA. All rights reserved
0741-8329/95 $9.50 + .00

0741-8329(95)02002-L

Effect of Acute Alcohol Intoxication on the Opioid System in Humans

J. C. AGUIRRE,* J. L. DEL ARBOL,*[1] J. RICO,* J. RAYA* AND M. E. RUIZ-REQUENA†

*Departments of *Medicine, and †Biochemistry and Molecular Biology, School of Medicine, University of Granada, E-18071 Granada, Spain*

Received 29 September 1994; Accepted 19 May 1995

AGUIRRE, J. C., J. L. DEL ARBOL, J. RICO, J. RAYA AND M. E. RUIZ-REQUENA. *Effect of acute alcohol intoxication on the opioid system in humans.* ALCOHOL 12(6) 559–562, 1995. – We investigated the possible relation between the endogenous opioid system and acute alcoholic intoxication in 21 subjects, of whom 13 were drinkers who came to the emergency service with evident symptoms of drunkenness, and 8 were nondrinkers who consumed 1 g alcohol per kg body weight over a short period. Different patterns of changes were found in the two groups for plasma concentrations of β-endorphin and adrenocorticotropic hormone. In drinkers, plasma levels of both substances increased, whereas in nondrinkers both concentrations decreased, the declines being especially notable 15, 30, and 45 min after ingestion. We found no differences between the two groups in plasma cortisol concentrations. The different levels of these substances may reflect differences in drinking behavior between the two groups.

Acute alcohol intoxication Adrenocorticotropic hormone Alcoholemia β-Endorphin Cortisol

ACUTE alcoholic intoxication (AAI) has been intensively studied to elucidate the mechanisms involved in its appearance and treatment. The effects of alcohol on the central nervous system in AAI have been investigated from several approaches, including its influence on the cell membrane (12,33,44), and more specifically, its effect on three types of neurotransmitter: opioid peptides (7,8,21,23,47), GABA (29,31), and catecholamines (11,32). Although the effects of alcohol on the cell membrane are well known, its effect on specific neurotransmitters is controversial, particularly in the case of endogenous opioids (19).

After the discovery of opioid peptides and their receptors, many researchers hypothesized that some of the effects of alcohol might arise from its influence on endogenous opioids (3,5,9,34,35,45). Studies of the connection between these peptides and chronic alcohol consumption (10,14,18,30) have related a deficit in β-endorphin (β-END) with some degree of predisposition toward alcohol consumption, in light of the finding that chronic alcoholics (1,2,7,15) and their relatives have lower basal levels of this endogenous opioid than controls (4).

There appears to be no set pattern in the effects of AAI on the opioid system: although most authors suggest that the acute administration of alcohol raised plasma concentrations of β-END, possibly by enhancing secretion by the pituitary (7, 22,24), others have reported differences related with the degree of aversion to alcohol consumption (6,26). In experimental animals, β-END secretion is greater when alcohol is consumed voluntarily than when it arouses aversion (7,16,17,27).

In humans, only persons at high risk for becoming alcohol abusers (i.e., persons with a family history of alcohol abuse for three generations) show increased basal levels of β-END after the ingestion of 0.5 g alcohol/kg body weight; basal concentration does not change in low-risk subjects (25). These findings suggest that there may be genetically determined differences in the response of the endogenous opioid system (EOS) to the acute ingestion of a moderate to large dose of alcohol. Such variations may be partially responsible for the differences between individuals in drinking behavior (16,17, 25,27).

The present study was thus designed to investigate the effect of AAI on plasma concentrations of β-END, adrenocorticotropic hormone (ACTH), and cortisol in persons who consumed alcohol voluntarily, and in nondrinkers given a dose of 1 g alcohol per kg body weight.

METHOD

We studied AAI in a total of 21 persons, who were divided into two groups. The first group (uncontrolled intoxication)

[1] Requests for reprints should be addressed to Dr. J. L. del Arbol, Carrera del Genil 35, 18009 Granada, Spain.

comprised 13 subjects (10 men, 3 women) ranging in age from 17 to 25 years (mean age 19.8 ± 2.6 years). All subjects in this group came to the emergency service with evident symptoms of drunkenness, which were considered to preclude the possibility of their experiencing stress during the intervention. We could not determine the amount consumed or the exact time elapsed between ingestion and arrival at the emergency room, although their clinical symptoms suggested that this interval was not very long. On questioning after the symptoms had remitted, all subjects admitted to being habitual drinkers, although on the basis of responses on questionnaires and tests (MAST, CAGE, and MALT), none could be classified as an alcoholic (40,43). Blood was collected from each subject between 0700 and 1000 h.

The second group (controlled intoxication) was selected in an attempt to identify the variables that influenced AAI (amount of alcohol consumed, duration of drinking, etc). We studied eight volunteers (six men, two women, mean age 22.8 ± 2.76 years), in whom daily consumption was nil or less than 10 g of alcohol. All participants gave their informed consent to take part in this part of the study, which was done in accordance with the guidelines of the Declaration of Helsinki, under the approval of our hospital's ethical committee. The scores on questionnaires designed to detect alcohol abuser were below mean values for the age group studied. None consumed alcohol during the 48 h before the study. On the day of the study they were asked to come to the hospital at 1000 h; at 1030 h a catheter was placed in an arm vein, and a light breakfast was served (25) to ensure that absorption was complete in all subjects, and to avoid the nausea that may result from alcohol intake on an empty stomach. [Nausea can be a source of stress, and may thus affect the results (38,39)]. A mixture of orange juice and 40% alcohol (80-proof gin) was prepared to produce a concentration of 1 g alcohol per kg body weight. The subjects were told to consume the drink in not more than 5 min.

Venous blood samples were drawn from each subject before the drink was consumed (basal), and 15, 30, 45, 120 min, and 24 h later. All subjects were under medical surveillance throughout the study. Subjects who were receiving any medical treatment, or whose laboratory results were suggestive of alcoholism, were excluded from the study.

The control group consisted of 80 apparently healthy subjects (mean age 44.37 ± 11.04 years) whose daily consumption was nil or less than 10–15 g of alcohol. None of the subjects had consumed alcohol during the 48 h prior to testing. All participants were included in the study in accordance with the same criteria as in the controlled group. The difference in mean age between the controls and the two experimental groups was considered not to affect the results of the analyses used here (20). All blood samples were obtained between 0830 and 0930 h.

Radioimmunoassay (RIA) was used to measure plasma concentrations of β-END (Allegro, Nicholas Institute, San Juan Capistrano, CA), ACTH (ACTH-PR, Oris SA, Gif-Sur-Yvette, France), and cortisol (Cort-CTk-2, Sorin Biomédica, Madrid, Spain). The intra-assay and interassay coefficients of variation were 4.1% and 7.7% for the β-END RIA, 2.1% and 1.3% for the ACTH kit, and 5% and 4.9% for the cortisol kit. The detection limits were 10 pg/ml for β-END, 2 pg/ml for ACTH, and 4.7 ng/ml for cortisol.

In the controlled intoxication group, alcoholemia was also measured in each of the six blood samples. In the uncontrolled intoxication group, alcoholemia was markedly greater than 2 g/l.

The data were analyzed with the 2D procedure of the Biomedical DP statistics package (BMDP), involving a descriptive study of the data, and determination of normality with Shapiro and Wilk's test. The changes in the results with time elapsed after alcohol consumption were compared with Friedman's test. Multiple comparisons between sampling times and between the uncontrolled intoxication and control groups were also analyzed with the Tukey method.

RESULTS

In the Uncontrolled intoxication group, mean plasma concentration of β- END was 48.3 ± 6.1 pg/ml, and mean plasma concentration of ACTH was 99.3 ± 26.4 pg/ml (Fig. 1). The concentrations of the different peptides in the controlled intoxication group at each sampling time are shown in Fig. 2. In the control group, the mean plasma level of β-END was 39.31 ± 3.44 pg/ml, the mean value for ACTH was 13.27 ± 1.85 pg/ml, and mean cortisol concentration in plasma was 17.22 ± 0.64 ng/ml.

Figure 3 contrasts the evolution of β-END and ACTH concentrations in the controlled intoxication group with the results in the uncontrolled intoxication and control groups. Basal values in the controlled intoxication and control groups did not differ significantly. In the group subjected to controlled AAI, β-END and ACTH showed similar patterns of changes with time, with low values 15, 30, and 45 min after alcohol ingestion. The clearest decrease was seen between 15 and 30 min postingestion. The difference from control values was significant for β-END ($p < 0.05$) measured at 30 and 45 min; no significant differences were found for ACTH ($p < 0.1$) (Fig. 2).

Plasma cortisol concentrations remained fairly stable throughout the experimental period. Alcoholemia reached peak concentrations after 45 min, decreasing thereafter and returning to basal values by 24 h postingestion. In fact, all parameters had returned to basal values 24 h after alcohol intake.

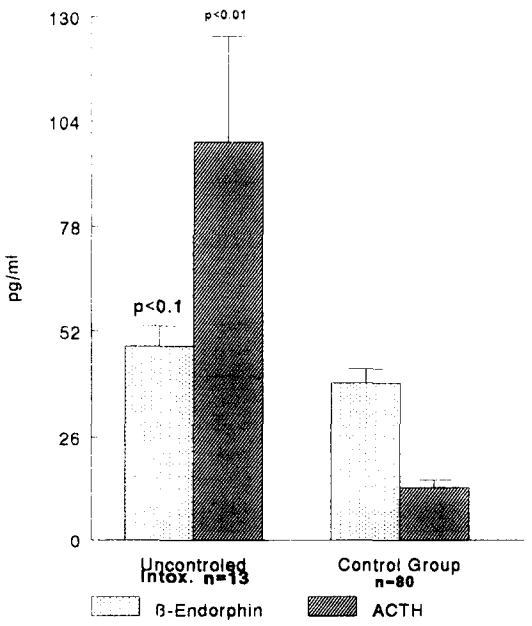

FIG. 1. Plasma concentrations of β-endorphin and ACTH in 80 control subjects and 13 habitual drinkers with acute alcoholic intoxication (uncontrolled intoxication). In the latter group, ACTH was significantly increased ($p < 0.01$), whereas β-endorphin increased in a nonsignificant manner.

As Figure 3 shows, different trends were apparent in controlled and uncontrolled intoxication. In nondrinkers given 1 g of alcohol per kg body weight, plasma β-END and ACTH decreased, whereas in "voluntarily" intoxicated subjects, these concentrations were higher than in the control group, although the difference was significant only for ACTH. The greatest differences between the controlled and uncontrolled groups occurred 30 and 45 min after ingestion.

DISCUSSION

The consumption of a moderately high dose of alcohol by persons who describe themselves as voluntary drinkers enhances the release of β-END and ACTH to the bloodstream. In contrast, alcohol intake by nondrinkers is followed within 15 min by a decrease in the plasma concentrations of these substances to below basal levels, with maximum decreases appearing after 30 min. The different responses of β-END may reflect different sensations of well-being (28), or indifference to alcohol intake in these two groups (16,17,27).

Our findings are similar to most results of earlier studies. Several authors have reported increased β-END secretion in response to an ethanol overload in rats that voluntarily consume alcohol, in comparison with animals for which alcohol was aversive (7,24,26). Similar reports in humans have noted that different values distinguished between subjects at high and low risk for developing alcohol dependence (25). In contrast, Naber et al. (36) gave 1 mg of an 80% alcoholic drink per kg body weight to four male nondrinkers, and found that acute alcohol consumption increased opioid activity by 400%, but did not significantly change plasma concentrations of β-END, possibly because of the low dose of alcohol administered.

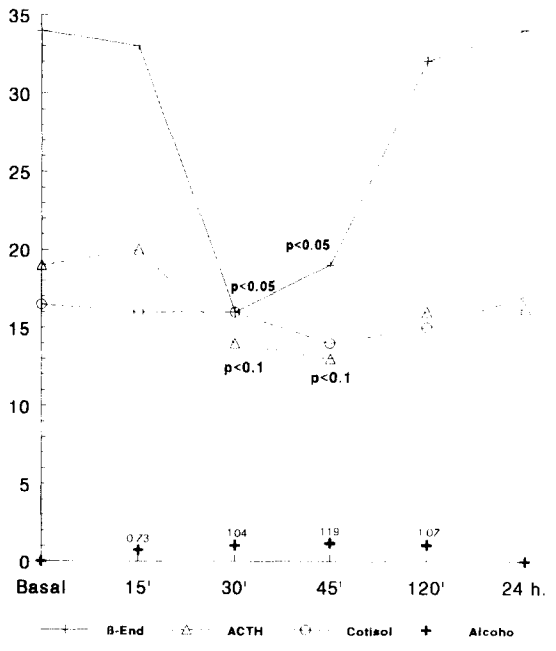

FIG. 2. Evolution of alcoholemia and plasma concentrations of β-endorphin, ACTH, and cortisol in eight nondrinkers given 1 g alcohol per kg body weight. Cortisol levels remained unchanged. β-Endorphin was significantly decreased, especially at 30 and 45 min ($p < 0.05$), coinciding with maximum alcoholemia. However, ACTH showed only a tendency to decrease. The y-axis shows values for β-endorphin and ACTH in pg/mL, cortisol in ng/mL, and alcohol in g/L.

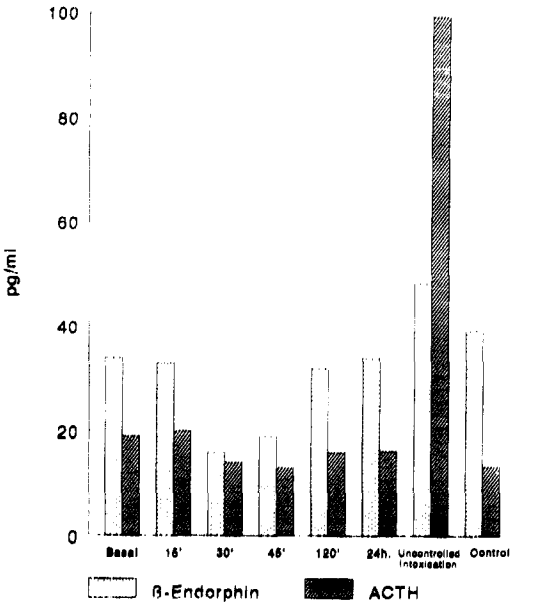

FIG. 3. Evolution of plasma concentrations of β-endorphin and ACTH in 8 nondrinkers given 1 g alcohol per kg body weight (controlled intoxication), in 13 habitual drinkers with acute alcoholic intoxication (uncontrolled intoxication), and 80 control subjects. Different patterns of changes were found in both β-END and ACTH levels. In voluntary drinkers, both peptides increased significantly, with the greater increase in ACTH; in nondrinkers, β-END was significantly decreased 30 and 45 min after ingestion, and ACTH showed a nonsignificant decrease. Both values had returned to normal by 24 h postingestion.

We found no previous reports of an association between AAI and ACTH concentrations. Although ACTH and β-END share the same precursor molecule (13,25,46), they may not be released into the bloodstream simultaneously, due to the effect of alcohol pe se, or because of alcohol-induced changes in their metabolism. The ACTH/β-END ratio in our group of habitual drinkers was of the opposite sign of that in the other two groups, a finding that may reflect the different stimulation by alcohol in drinkers and nondrinkers.

The behavior of cortisol in the present study contrasts with the findings of an earlier report (25). However, the results of the two studies are not entirely comparable, as we did not measure cortisol concentrations in one of our experimental groups (uncontrolled intoxication). Controlled intoxication with 1 g of alcohol per kg body weight in "low-risk" subjects led to a slight decrease in plasma cortisol concentrations, possibly because of a direct action of alcohol on the adrenal cortex, or through a secondary effect via the decrease in ACTH levels. However, if the second hypothesis was true, we should have found increased plasma cortisol levels in the uncontrolled intoxication group, as reported by gianoulakis et al. (25), In view of the high plasma concentrations of ACTH (37).

In conclusion, we found differences between nondrinkers and persons habituated to alcohol in the release of β-END and ACTH into the bloodstream. These discrepancies may partially account for the different drinking behaviors in these two groups of individuals.

ACKNOWLEDGEMENTS

This study was supported by the education and science council of the andalusian regional government project no. 3001. We thank Ms Karen Shashok for translating the original manuscript into English.

REFERENCES

1. Aguirre, J. C.; Del Arbol, J. L.; Raya, J.; Ruiz, M. E.; Rico, J. Plasma β-endorphin levels in chronic alcoholics. Alcohol 7:409-412; 1990
2. Aguirre, J. C.; Del Arbol, J. L.; Raya, J.; Ruiz, M. E.; Rico, J. Derivados de la pro-opiomelanocortina (ACTH y β-endorfina) en alcohólicos crónicos. An. Med. Interna 8(5):228-232; 1991.
3. Blum, K. A commentary on ethanol-neuromodulator mechanism: Theoretical and clinical implications. In: Nappi, G., ed. Neurodegenerative disorders: The role played by endotoxins and xenobiotics. New York: Raven Press; 1988:269-285..
4. Blum, K. The disease process in alcoholism. Aidsm, alcohol & drugs. Alcohol. Addict. May-June; 1988.
5. Blum, K.; Briggs, A. Opioid peptides and genotypic responses to ethanol. Biogenic Amines 5(6):527-533; 1988.
6. Blum, K.; Briggs, A. H.; Trachtenberg, M.; De Lallo, L.; Wallace, J. E. Enkephalinase inhibition: Regulation of ethanol intake in genetically predisposed mice. Alcohol 4(6):449-456; 1987.
7. Blum, K.; Topel, H. Opioid peptides and alcoholism: Genetic deficiency and chemical management. Funct. Neurol. 1(1):71-83; 1986.
8. Blum, K.; Trachtenberg, M. C. Alcoholism: Scientific basis of a neuropsychogenetic disease. Int. J. Addict. 23(8):781-796; 1988.
9. Blum, K.; Trachtenberg, M. C. Neurogenetic deficits caused by alcoholism: Restoration by SAAVETM, a neuronutrient intervention adjunct. J. Psychoact. Drugs 20(3):297-313; 1988.
10. Burov, V. G.; Treskov, R.; Yukhananov, A. E.; Kovalenko, R. Blood β-endorphines and endogenous ethanol in alcoholics. Biull. Eksp. Biol. Med. 98(11):578-579; 1984.
11. Cacabelos, R. Bases neurológicas de la adicción alcohólica. Jano 900:1371-1391; 1990.
12. Chin, J. H.; Goldstein, D. B. Effects of low concentrations of ethanol on the fluidity of spin-labeled erythrocytes and brain mambranes. Mol. Pharmacol. 13:435-441; 1977.
13. Craig, S.; Pickard, D.; Barchas, J. D.; Berger, P. A. Symposium on endorphins. Psychiatr. Clin. North Am. 6(3):353-523; 1983.
14. Dave, J. R.; Karanian, J. W.; Eskay, R. L. Chronic ethanol treatment decreases specific nonopiate β-endorphin binding to hepatic and kidney membranes and lowers plasma β-endorphin in the rat. Alcohol. Clin. Exp. Res. 10(2):161-166; 1986.
15. Del Arbol, J. L.; Aguirre, J. C.; Raya, J.; Ruiz, M. E.; Rico, J. Derivados de la POMC en alcohólicos crónicos. An. Med. Interna VI:50-51; 1989.
16. De Waele, J. P.; Gianoulakis, C. Effects of single and repeated exposures to ethanol on hypothalamic β-endorphin and CRH release by the C57BL/6 and DBA/2 strains of mice. Neuroendocrinology 57(4):700-709; 1993.
17. De Waele, J. P.; Papachristou, D. N.; Gianoulakis, C. The alcohol-preferring C57BL/6 mice present an enhanced sensitivity of the hypothalamic β-endorphin system to ethanol than the alcohol-avoiding DBA/2 mice. J. Pharmacol. Exp. Ther. 261(2):788-794; 1992.
18. Facchinetti, F.; Petraglia, F.; Nappi, G.; Martignoni, E.; Sinforiani, E.; Bono, G.; Genazzani, A. R. Functional opioid activity variates according to the different fashion of alcohol abuse. Subst. Alcohol Actions Misuse 5:281-291; 1985.
19. Fernández del Moral, R.; Dawid-Milner, S.; Diaz-Calavia, E. J. Farmacología de la intoxicación alcohólica aguda. Inflamación 3: 570-577; 1992.
20. Forman, L. J.; Cavalieri, T.; Fitzharris, J.; Chopra, A.; Marquis, D.; Estilow, S. Plasma levels of beta-endorphin in young and aged human males during morning hours. Horm. Metab. Res. 19: 38-39; 1987.
21. Froehlich, J. C.; Zwifel, M.; Harts, J.; Lumeng, L.; Li, T. K. Importance of delta opioid receptors in maintaining high alcohol drinking. Psychopharmacology (Berlin) 103(4):467-472; 1991.
22. Gianoulakis, C. Characterization of the effects of acute ethanol administration on the release of β-endorphin peptides by the rat hypothalamus. Eur. J. Pharmacol. 180(1):21-29; 1990.
23. Gianoulakis, C. Endogenous opioids and excessive alcohol consumption. J. Psychiatry Neurosci. 18(4):148-156; 1993.
24. Gianoulakis, C.; Barcomb, A. Effect of acute ethanol in vivo and in vitro on the β-endorphin system in the rat. Life Sci. 40(1):19-28; 1987.
25. Gianoulakis, C.; Beliveau, D.; Angelogianni, P.; Meaney, M.; Thavundayil, J.; Tawar, V.; Dumas, M. Different pituitary β-endorphin and adrenal cortisol response to ethanol in individuals with high and low risk for future development of alcoholism. Life Sci. 45(12):1097-1109; 1989.
26. Gianoulakis, C.; Gupta, A. Inbred strains of mice with variable sensitivity to ethanol exhibit differences in the content and processing of β-endorphin. Life Sci. 39(4):1315-1325; 1986.
27. Gianoulakis, C.; De Waele, J. P.; Kiianmaa, K. Differences in the brain and pituitary β-endorphin system between the alcohol-preferring AA and alcohol-avoiding ANA rats. Alcohol. Clin. Exp. Res. 16(3):453-459; 1992.
28. Hawkes, C. H. Endorphins: The basis of pleasure? J. Neurol. Neurosurg. Psychiatry 55.247-250; 1992.
29. Hut, W. A.; Wixon, Hn.; Dalton, T. K. Studies of gabaergic transmission in brain after acute and chronic administration of ethanol. Fed. Proc. 39:993; 1980.
30. Jitendra, R.; Eiden, L. E.; Karanian, J. W.; Eskay, R. L. Ethanol exposure decreases pituitary corticotropin-releasing factor binding, adenylate cyclase activity, proopiomelanocortin biosynthesis and plasma β-endorphin levels in the rat. Endocrinology 118(1): 280-287; 1986.
31. Krupitsky, E. M.; Burakov, A. M.; Karandashova, G. F.; Katsnelson, J. S.; Lebedev, V. P.; Grinenko, A. J.; Borodkin, Ju. S. The administration of transcranial electric treatment for affective disturbances therapy in alcoholic patients. Drug Alcohol Depend. 27(1):1-6; 1991.
32. Linnoila, M.; Medford, I.; Nutt, D.; Adinoff, B. Alcohol withdrawal and noradrenergic function. Ann. Intern. Med. 107:875-889; 1987.
33. McCreery, M. J.; Hunt, W. A. Physico-chemical correlates of alcohol intoxication. Neuropharmacology 17:451-461; 1978.
34. Myers, R. D.; Melchior, C. L. Alcohol drinking: Abnormal intake caused by tetrahydropapaveroline in brain. Science 196:554-556; 1977.
35. Myers, R. D.; Privette, T. H. A neuroanatomical substrate for alcohol drinking: Identification of tetrahydropapaveroline (THP)-reactive sites in the rat brain. Brain Res. Bull. 22:899-911; 1989.
36. Naber, D.; Sobl, M. G.; Pickard, D. Ethanol increases opioid activity inplasma of normal volunteers. Pharmacopsychiatria 14: 160-161; 1981.
37. Noth, R. H.; Walter, R. H. Efectos del alcohol sobre el sistema endocrino. Med. Clin. North Am. 68:133-146; 1984.
38. Olson, G. A.; Olson, R. D.; Kastin, A. J. Review: Endogenous opiates: 1986. Peptides 8(6):1135-1164; 1987.
39. Owens, P. C.; Smith, R. Opioid peptides in blood and cerebrospinal fluid during acute stress. In: Clinical endocrinology and metabolism. Neuroendocrinology of stress. 1:415-437; 1987.
40. Paton, A.; Saunders, J. B. Asking the right questions. Br. Med. J. 283:1458-1459; 1981.
41. Rodríguez-Martos, A.; Suarez Vazquez, R. MALT (Münchner Alkoholismus Test): Validación de la versión española de este test para el diagnóstico del alcoholismo. Rev. Psiquiat. Psicol. Med. 6(16):421-432; 1984.
42. Rueff, B.; Crnac, J.; Darne, B. Detection of alcoholic patients with CAGE questionaries in 200 patients. Presse Med. 18(33): 1654-1656; 1989.
43. Selzer, M. The Michigan Alcoholism Screening Test: The quest for a new diagnostic instrument. Am. J. Psychiatr. 127(12):1653-1658; 1971.
44. Suzdak, P. D.; Glowa, J. R.; Crawley, J. N.; Schwartz, R. D.; Skolnick, P.; Paul, S. M. A selective imidazobenzodiazepine antagonist of ethanol in the rat. Science 234:1243-1247; 1986.
45. Trachtenberg, M.; Blum, K. Alcohol and opioid peptides: Neuropharmacological rationale for physical craving of alcohol. Am. J. Drug Alcohol Abuse 13(3):365-372; 1987.
46. Weber, E.; Evans, C. J.; Barchas, J. D. Multiple endogenous ligands for opioid receptors. Trends Neurosci. 6:333-336; 1983.
47. Widdowson, P. S.; Holman, R. B. Ethanol induced increase in endogenous dopamine release may involve endogenous opiates. J. Neurochem. 59(1):157-163; 1992.