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Effect of Naloxone on Acute Ethylic Intoxication. An EEG Study

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EEG recording has been used to evaluate in cats the effect of naloxone on acute ethylic intoxication (AEI). Naloxone was administered both before and during the course of AEI. Results of the experiment showed that administration of naloxone before the AEI potentiates the toxic effect of alcohol. However, the administration of naloxone in a continuous way along the course of AEI significantly diminished the toxic effect of alcohol.

Key words: Alcohol, Naloxone, EEG.

Several investigators have recently suggested that alcohol effects might be related to either the release of endogenous opioids or the synthesis of opioid compounds (1, 10). On the basis of this hypothesis many clinical and experimental investigations (2, 3, 6, 7, 12) have been carried out; this is especially relevant on the ground of the specific antagonistic effect of naloxone on opioid receptors in cases of acute ethylic intoxication (AEI). Results are relatively contradictory and the effect of naloxone on AEI as well as its mechanism of action remain to be completely elucidated.

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The goal of this work is to investigate in cats the effect of naloxone on AEI by means of EEG recording. It has been found that naloxone administered before the AEI potentiates the toxic effects of alcohol; however, when naloxone is given in a continuous way during the course of AEI, the toxic effects of alcohol are outstandingly reduced.

Materials and Methods

This experiment was conducted in 21 adult cats weighing about 4 kg, with chronic electrodes Ag/AgCl implanted in the duramater in P3P4 (area 17).

The signal was filtered 0.1 to 100 Hz

and amplified × 100 by means of a differential amplifier Keithley 103A. The graphic register was obtained through a polygraph Beckman. Both EEG and respiratory frequency were registered, the latter through a nasal thermistor. The alcohol was administered by continuous i.v. perfusion of a glucose physiological solution (5 %) at a 0.06 g · kg^{-1} · min^{-1} dose.

The work was performed on three groups of cats systematically analyzing the mean EEG frequency (mEF) as follows: 1) Continuous perfusion of alcohol (3 h). 2) Naloxone administration (400 µg · kg^{-1} body weight) 10 min before the alcohol perfusion. 3) Naloxone administration (same dose as above) 10 min before, at the beginning and everey 10 min during the alcohol perfusion.

Taking into account this way of registering the EEG, the occasional influence of factors which could interfere by creating artefacts could be considered negligible.

Statistical analysis was carried out computing the mean values (± SD) of the mEF during the experiment. Once the statistical normality (D'Agostino's test) was verified as well as the homocedasticity (Bartlett's test) of the data, an analysis of the variance (ANOVA) was made; this ANOVA was calculated for two functions, one being the mEF and the other the total amount of alcohol administered. Statistically significant differences were calculated by the Student's *t* test.

Results

Results of the experiment are summarized in fig. 1. Alcohol perfusion produced an immediate and progressive decrease of the mEF, this decrease being especially marked in the animals receiving the highest dose of alcohol; it is of interest to point out that doses of about 4.12 g · kg^{-1} brought about a flat EEG.

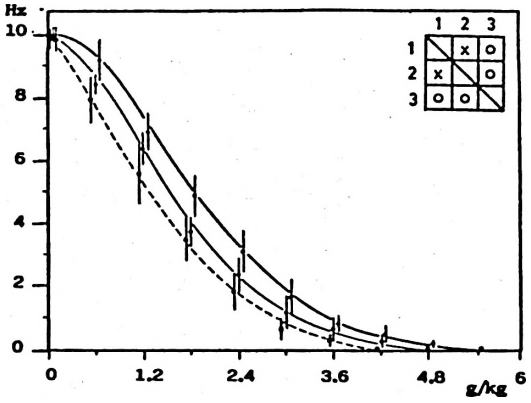

Fig. 1. *Median frequency changes (Hz) of the EEG in cats.*
Group 1 (——), continuous perfusion (3 h) of alcohol (0.06 g · kg^{-1} body weight · min^{-1}). Group 2 (---), identical to group 1, with the exception that naloxone (400 µg · kg^{-1} body weight) was given during 10 min before alcohol perfusion. Group 3 (——), as described in group 2, with the exception that naloxone was also given, at the indicated dose, every 10 min throughout the 3 h alcohol perfusion. Statistical differences are summarized in the square at the right top of the figure. Symbols mean: (x) $p < 0.05$, (o) $p < 0.01$.

Naloxone administration 10 min before the alcohol perfusion produced a significant reduction of the mEF throughout the experimental period; however, it is noteworthy to emphasize that in this case the flat EEG is achieved at alcohol concentrations lesser than those needed when ethanol is administered alone.

When naloxone is given both before and after alcoholic perfusion an opposite picture is observed; the flat EEG is achieved when plasma alcohol concentration reached its highest value.

Statistical relevance of these differences are given in fig. 1.

Discussion

Results of this experiment showed that the changes of mEF associated with AEI

were similar to those already described (7).

Naloxone administration just before the AEI increased the alcohol toxic effects, whereas naloxone administration both before and during AEI reduced them.

It is thought that naloxone (antagonistic substance to the opioid receptors) causes a transient increase on the density of μ opioid receptors (8, 9); this effect is manifested 5 min after the drug administration and it is roughly maintained during 2 h. It is of interest to indicate that this change affects only receptor density and not their affinity. The precise mechanism is not completely understood, but it seems possible that two populations of receptors might be there in equilibrium: the so called active and silent receptors. Naloxone would block active receptors by an unknown mechanism, through which it would lead to an activation of silent receptors.

On the other hand, naloxone effect is dependent upon its half life and therefore, after the blocking action reaches its maximal effect during the first 5-10 min, it decreases; this effect is accompanied by an increase in the number of active receptors (9). It could be thought that in the conditions of this study, the number of receptors in the animals receiving naloxone before the perfusion of alcohol is higher at the beginning of the experimental period than afterwards.

Alcohol administration is known to increase the release of endogenous opioids in some brain areas (11); furthermore, acetaldehyde —ethanol metabolite— through the P-S reactions reacts with dopamine, which produce tetrahydroisoquinoleins, which bind themselves to opioid receptors (especially, μ receptors) (5).

Concentrations of both opioids and tetrahydroisoquinoleins can be thought to increase in a similar way in the three experimental groups, since the effect depends basically on alcohol concentration; in this case, the toxic effect of alcohol would be the corresponding to a higher dose of alcohol.

However, when naloxone is administered both before and during alcohol perfusion the blocking effect is maintained and, therefore, the toxic effect would be inferior in spite an increase in the receptor population.

In conclusion, the results of this experiment clearly show that naloxone antagonizes the toxic alcohol effect —as measured by mEF— only when it is given few minutes before alcohol perfusion. Further experimental work is needed in order to throw more light on the antagonistic effect between alcohol and naloxone.

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Resumen

Se utiliza el registro del EEG con objeto de determinar en gatos el efecto de la naloxona en la intoxicación etílica aguda (IEA). La naloxona se administra con anterioridad, durante y después de instaurar en los animales un estado de IEA. Los resultados muestran que la administración de naloxona antes de la IEA potencia los efectos tóxicos del alcohol y que administrada de forma continua durante todo el tiempo de IEA reduce esos efectos tóxicos.

Palabras clave: Alcohol, Naloxona, EEG.

References

1. Blum, K., Futterman, S., Wallace, J. E. and Schwertner, H. A.: *Nature*, 265, 49-51, 1977.
2. Catley, D. H., Jordan, C., Frith, C. D., Lehane, J. R., Rhodes, A. M. and Jones, J. C.: *Psycopharmacology*, 75, 65-68, 1981.
3. Docobu, J.: *Ann. Intern. Med.*, 100, 617-618, 1984.
4. Hamilton, M. G. and Hirst, M.: *Substances Alcohol Misuse*, 1, 121-126, 1980.

5. Luchi, L., Rius, R. A., Uzumaki, H., Govoni, S. and Trabucchi, M.: *Brain Res.*, 293, 368-371, 1984.
6. Luttinger, D., Frye, G. D., Nemeroff, C. B. and Prange Jr., A. J.: *Psycopharmacology*, 79, 357-363, 1983.
7. McGivern, R. F., Harris, J. M., Yessaian, N., Kastin, A. J., Coy, D. H., Sandman, C. A. and Noble, E. P.: *Substances Alcohol Misuse*, 1, 335-342, 1980.
8. Pert, C. B., Pasternack, G. and Snyder, S. H.: *Science*, 182, 1359-1361, 1973.
9. Pert, C. B. and Snyder, S.: *Biochem. Pharmacol.*, 25, 847-853, 1976.
10. Ross, D. H.: *Ann. N.Y. Acad. Sci.*, 273, 280-293, 1976.
11. Schulz, R., Wuster, M., Duka, T. and Herz, A.: *Psycopharmacology*, 68, 221-227, 1980.
12. Whalley, L. J., Freeman, C. P. and Hunter, J.: *Lancet*, ii, 89, 1981.