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Electroencephalographic Study of Naloxone Effects in the Recovery of an Acute Alcoholic Intoxication

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Experimental assays analysing EEG changes during the recovery of an acute alcoholic intoxication were carried out in three groups of cats: 1) Recovery of acute alcoholic intoxication produced by continuous intravenous perfusion of ethanol, 0.06 g/kg/min, during 20 minutes. 2) Recovery of acute alcoholic intoxication by injecting naloxone (400 µg/kg), just after finishing alcohol perfusion. 3) Recovery of acute alcoholic intoxication by injecting naloxone (400 µg/kg), 15 min after finishing perfusion. Naloxone administered after an acute alcoholic intoxication worsens the recovery of EEG parameters; 1-2 ($p < 0.05$), 1-3 ($p < 0.05$).

Key words: EEG, Naloxone, Alcoholic intoxication, Cat.

During the last decade several authors have suggested that the toxic effects of ethanol could be partially mediated through the release of endogenous opiates or by the formation of opiatelike compounds (1).

Working from this hypothesis several clinical assays and various experiences in experimental animals and human volunteers have been made, by analysing the effects of naloxone, a µ opiate receptor antagonist, in the treatment of the acute alcoholic intoxication. The results obtained are contradictory and in some cases disparate (2, 4, 6, 7, 10), leading to the conclusion that the possible role of endogenous opiates in the acute alcoholic intoxication is still an objective of investigation.

In this paper we have studied by means of EEG the effects of naloxone during the recovery of an acute alcoholic intoxication produced in cats.

Materials and Methods

Eighteen adult cats, weighing between 3 and 4 kg (3.55 ± 0.33 SD), with chronic

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electrodes Ag/AgCl implanted over the dura at coordinates 21 mm from the bregma and 3 mm right from the midline (P4), were used, with a frontal electrode as reference. The signal was filtered (0.1-100 Hz) and amplified (× 100) by means of a Keithley 103A differential amplifier and recorded in a Beckman poligraph. Alcohol was administered by sustained intravenous perfusion of a 20 % solution in 5 % glucose serum at a dosis of 0.06 g/kg/min.

It was assumed that naloxone administered during an acute alcoholic intoxication recovery would block opiate receptor sites, thus neutralising the ethanol effects depending on opiate or isoquinoline levels. In agreement with this hypothesis experimental assays in three groups of cats were carried out by analysing EEG frequency: 1) Recovery of an acute alcoholic intoxication produced by continuous intravenous perfusion of ethanol during 20 min. 2) Recovery of an acute alcoholic intoxication produced as in the first group, by injecting naloxone (400 μg/kg), just after finishing ethanol perfusion. 3) Recovery of an acute alcoholic intoxication produced as in the first group, by injecting naloxone (400 μg/kg), 15 min after finishing ethanol perfusion.

For statistical procedures all cats were included in the results, the mean EEG frequency and its standard deviation obtained during the experiments were calculated. Comparisons were made through the covariance test, while the t test was also performed when required.

Results

The changes observed in EEG mean frequency in the three groups during the recovery of an acute alcoholic intoxication are shown in figure 1. Alcohol perfusion during 20 min produces a decrease of EEG mean frequency to Θ frequency, which is

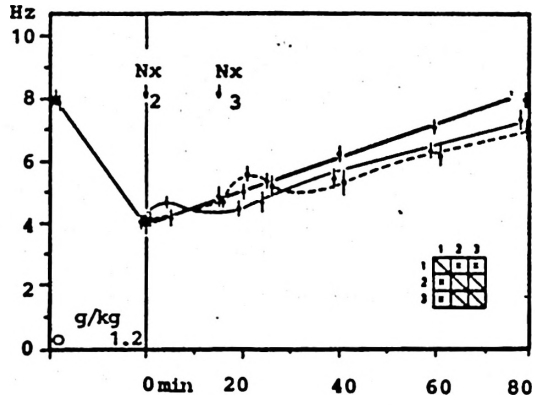

Fig. 1. *Changes of EEG mean frequency (Hz) in experimental groups.*
1) (—) Spontaneous recovery of acute alcoholic intoxication (g/kg, dosis of ethanol perfused; min, recovery time). 2) (—) Recovery of acute alcoholic intoxication injecting naloxone (Nx) just after finishing perfusion. 3) (---) Recovery of acute alcoholic intoxication injecting naloxone 15 min after finishing ethanol perfusion. In left bottom square statistical summary; (x) $p < 0.05$.

significant in the three groups ($p < 0.001$), but without significant differences between groups.

After finishing ethanol perfusion a spontaneous slow and linear increase in EEG mean frequency was produced in group 1. EEG mean frequency values, which were not significantly different from those obtained before initiating ethanol perfusion, were reached 75 min after finishing perfusion.

Naloxone produced in both groups (2 and 3), 5 min after its administration, an increase in EEG mean frequency which was significantly higher ($p < 0.02$, $p < 0.05$) than that observed in spontaneous recovery.

After the first excitatory phase of naloxone a second phase was produced, in which the increase in EEG mean frequency was slower than that observed in spontaneous recovery.

Ten minutes after the administration of

naloxone, EEG mean frequency values were similar to those obtained in spontaneous recovery, but 20 min after naloxone, EEG mean frequency values were significantly lower ($p < 0.05$). Significant differences ($0.05 > p > 0.01$) were maintained until minute 95 and 105 respectively, in which EEG mean frequency reached values that were not significantly different from those obtained before initiating alcohol perfusion.

The delay observed in the EEG recovery in groups receiving naloxone was due to the momentary appearance of δ waves 10 to 20 min after its administration.

The statistical study showed significant differences between groups; 1-2 ($p < 0.05$) and 1-3 ($p < 0.05$). No significant differences were obtained between naloxone groups 2-3 (fig. 1).

Discussion

The changes observed in EEG frequency during the recovery of an acute alcoholic intoxication are similar to those described elsewhere (3).

Naloxone administered after an acute alcoholic intoxication, in our experimental conditions, worsens the recovery of EEG parameters.

The administration of naloxone, a μ opiate receptor antagonist, produces an increase in the receptors density which appears 5 minutes after its administration and persists during, approximately 2 h (8). Although the mechanism is not known, it seems likely that there are two kinds of μ opiate receptors in equilibrium, active receptors and silent non active receptors. Naloxone blocking of active receptors leads to the activation of non active receptors. A decrease in the blocking effect of naloxone produces an increase in active receptors density.

The administration of ethanol increases endorphin in certain brain areas (9), and its metabolite, acetaldehyde, is condensed with dopamine generating salsolinol which binds μ opiate receptor sites (5).

In our experimental conditions the levels of endorphins and salsolinol in the three groups may be assumed to be the same, as this effect is dependent on ethanol levels and on its metabolic degradation. In the groups receiving naloxone and owing to the increase in μ opiate receptor density, with equal amounts of endorphins or salsolinol, the recovery of the EEG frequency should be subsequent to that of spontaneous recovery.

This hypothesis would explain the negative results observed after naloxone administration in the acute alcoholic intoxication treatment, but as in all hypotheses it will need confirmation in further reports.

Resumen

Se estudia por medio del EEG el efecto de la naloxona (400 μg/kg) en la recuperación de una intoxicación etílica aguda producida en tres grupos de gatos: 1) Recuperación de intoxicación etílica aguda producida por perfusión continua intravenosa de alcohol (0,06 g/kg/min) durante 20 minutos. 2) Recuperación de intoxicación etílica aguda inyectando naloxona, inmediatamente después de finalizar la perfusión de alcohol. 3) Recuperación de intoxicación etílica aguda inyectando naloxona, a los 15 minutos de finalizar la perfusión. En estas condiciones experimentales la administración de naloxona después de la intoxicación etílica aguda empeora el curso de la recuperación del EEG: 1-2 ($p < 0,05$), 1-3 ($p < 0,05$).

Palabras clave: EEG, Naloxona, Intoxicación etílica, Gato.

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