LOW ATROPINE DOSE INCREASES THE FREQUENCY OF HIPPOCAMPAL THETA ACTIVITY

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Abstract. The influence of two doses (6 and 3 mg/kg) of atropine (A) on hippocampal theta activity (TA) induced by means of reticular stimulation was studied in waking rats with implanted electrodes. The higher dose of A depressed TA and the lower dose reduced markedly its incidence. The frequency of TA remaining after A administration increased significantly. The results suggest that A acts in a different way upon the mechanisms responsible for the occurrence of TA and its frequency. An accidental finding was that A prolongs paroxysmal hippocampal EEG induced by reticular stimulation.

It has been found previously that atropine subcutaneous infusion of 12 mg/kg during 2 h decreases the incidence of hippocampal theta activity (TA) during paradoxical sleep but increases the frequency of the remaining TA in rats (15). Similar frequency changes after low atropine (A) doses have been observed in waking cats during learning (3). The aim of the present experiments was to analyze whether the frequency of TA increases after a sufficiently low dose of A simultaneously with the partial inhibition of TA and with its replacement by slow wave EEG (a finding known for many years — 10, 12, 13, 15, 16).

Experiment was performed on 10 unanesthetized freely moving rats with stereotaxically (1, 5) implanted bipolar electrodes (tip distance about 1 mm) in the dorsal hippocampus (coordinates A 3.5, L 3.5, V 4.0) for
recording TA and in the mesencephalic reticular formation (A 7.0, L 1.5, V 7.5) for stimulation by means of trains of 2 ms rectangular electrical pulses at a frequency of 200/s. Eight second stimulation and nonstimulation periods alternated regularly ten times at each stimulating voltage with one minute pause between different voltages. The voltage was increased in 0.5 V steps from 0.5 V until the threshold for evoking motor activity was reached (at about 2 V). EEG activity from the dorsal hippocampus was recorded on paper (both in native and band-path filtered form) and on magnetic tape, using a Bell Howel FM tape recorder for OFF-line computer analysis by means of a PDP 11/40. The incidence of TA (the proportion of stimulation respectively interstimulation period containing TA) and its frequency were measured by means of the computer (7), and the results evaluated statistically (one way ANOVA). The same procedure was performed before and after 10 and 60 min the administration of atropin sulphate (i.p.) as well as of saline.

Saline administration did not change the parameters of TA. Thus, the results of measurements before A administration could be used as control values and compared with those 10 and 60 min after A. Because signs of habituation of TA during the series of 10 consecutive stimuli were found only exceptionally, the values of measurements could be pooled together. Examples of EEG recordings are in Fig. 1. The main results of statistical evaluation are in Fig. 2. The 6 mg/kg A dose (10 experiments, 3 computer processed) reduced TA incidence 60 min after A administration almost to zero, whereas after 10 min no significant changes could be found. Thus the influence of A upon the TA frequency could not be analyzed after this dose in a reliable way. Sixty min after administration of 3 mg/kg of A the incidence of TA decreased markedly; the temporal sequence of waves was disturbed; and thus the EEG response to stimula-

![Fig. 1. Hippocampal theta activity during (event line in upper position) and without (event line in lower position) reticular stimulation. A, before; B, 10 min; C, 60 min after administration of 3 mg/kg (left) and 6 mg/kg (right) of atropine sulphate i.p.](image-url)
tion less conspicuous (10 experiments). Simultaneously the frequency of the remaining TA increased significantly by about 0.5 Hz. ANOVA statistics proved that the incidence of TA was higher after A when the voltage of reticular stimulation was higher in comparison with the trials in which low voltage stimuli were used. Thus, the desorganizing effect of A upon TA can be at least partially compensated by a higher level of reticular activation. However, the frequency of TA after A was practically equal, it increased to the same level without regard to the stimulating voltage or whether or not the reticular formation was stimulated or not. The results lead to the conclusion that A acts in a different way upon the mechanisms responsible for the occurrence of TA and its frequency. It is necessary to take into consideration, however, that the

![Fig. 2. Incidence (TA %) and frequency f(Hz) of hippocampal theta activity during stimulation (white columns) and alternating non-stimulation periods (striped columns). A, before; B, 10 min; C, 60 min after administration of 3 mg/kg (top) and 6 mg/kg (bottom) of atropine. Significant difference (P < 0.05) marked by horizontal lines below the columns. For details see text.](image)
change of frequency occurred within the range corresponding to the state of immobility (8, 9, 12). As motor activity evoked by reticular stimulation could influence TA secondarily, only stimulus voltage subthreshold with respect to induced movements could be used. During movements when TA frequency is higher (8, 9, 14) the influence of A might be different. The threshold for evoking motor activity by reticular stimulation did not change after A (2.3 ± 0.3 V after A vs. 2.5 ± 0.4 V after saline compared by the Wilcoxon test) in contradistinction to similar experiments with physostigmine in which the threshold decreased (4). For the above reasons it was not possible to answer the question whether the effect of A and reticular stimulation upon TA frequency is additive or not (see 4). The question addressed in these experiments required the use of low doses of A. Thus it would be difficult to compare our experiment with those in which higher A doses and similar compounds were used (2, 8, 11).

![Graph](image)

Fig. 3. Paroxysmal EEG activity induced by reticular stimulation. A, before; B, 10 min after 6 mg/kg of atropine; C, demonstrates that once started paroxysmal activity is not influenced by reticular stimulation (60 min after 6 mg/kg of atropine). For details see text.

In the majority of experiments (in 7 rats of 10) paroxysmal activity was sometimes seen in the hippocampal EEG (Fig. 3) during and after reticular stimulation (these recordings were excluded from TA evaluation). Its duration increased markedly 60 min after the administration of 6 mg/kg of A (from the mean of 34 s to more than 135 s — upper limit not established exactly as registration was stopped in some cases). Thus, cholinergic mechanisms seem to play a role in the maintenance of paroxysmal activity.
A preliminary report was read on the 1982 meeting of the Czechoslovak Society for the Study of Higher Nervous Activity (6).


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