Rhythmic Cerebellar and Cortical Electric Activity in Tetanus Intoxicated Rabbits[1]

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Summary. Intravenously injected tetanus toxin induced general tetanus within 12 to 37 h. The EEG of precentral, parietal, and occipital areas and of the cerebellum revealed a highly rhythmic activity. In local tetanus of the limbs or in brainstem tetanus this rhythm could not be registered.

According to previous papers, which only skim over this subject, no characteristic changes of the electroencephalogram (EEG) occur in the course of tetanus intoxication. Comparing the influence on cerebellar EEG of tetanus toxin and strychnine, Naquet et al.[2] found that the cerebellar EEG changes occurring under strychnine did not occur in tetanus-intoxicated cats. Regarding the cortical EEG no special experiments have been designed to reveal the modification of cortical activity by tetanus toxin. This paper deals with the influence of tetanus intoxication on cerebellar and cortical EEG of the rabbit.

Materials and methods. Experiments were performed on 30 male rabbits weighing between 1.6 and 3.6 kg. Two non-purified batches of tetanus toxin from the strains Kopenhagen 401 and 501A (Serotherapeutisches Institut Wien) and the highly purified OP-546/1 (Behringwerke, Marburg/Lahn) were used.

When general tetanus was the aim of experiments, 10^4 to 10^5 LD_{50} (*M*) were injected i.v. Surgical procedures were commenced under propanidid anesthesia and the animals were then immobilized by gallamine triethiodide or diallyl-bis-nor-toxiferine with the first convulsion, which occured 12 to 37 h following toxin administration, depending on the dose used. All wounds and pressure points were carefully infiltrated by 2% procaine hydrochloride. Recordings of precentral, parietal and occipital cortical areas and of anterior cerebellar lobe were made by conventional mehod. A spectral analysis of the recordings was estimated by means of a 5481 Hewlett-Packard Signal Analyzer System. Basically the method of Flühler[3] was used.

When local tetanus was intended, about 10^3 LD_{50} of toxin were injected into the biceps femoris of either hind leg and in some cases additionally into the flexor muscles of either forearm. In order to produce brainstem tetanus[4], this dose was injected into the rectus lateralis muscle of one eye. When torticollis, symptomatic of brainstem tetanus occured (within 1 and $1^1/_2$ days in our 2 experiments) or symptoms of local tetanus of the limbs appeared (within $1^1/_2$ to $3^1/_2$ days), surgical procedures were performed as described above.

Results. General tetanus. The EEG of all animals prepared with generalized convulsion revealed a cerebellar rhythm from the beginning of registration. This rhythm persisted throughout the experiment (Figure 1), without sudden changes in frequency and amplitude. The frequency range at the beginning varied between 18–34 Hz in the different experiments, falling progres-

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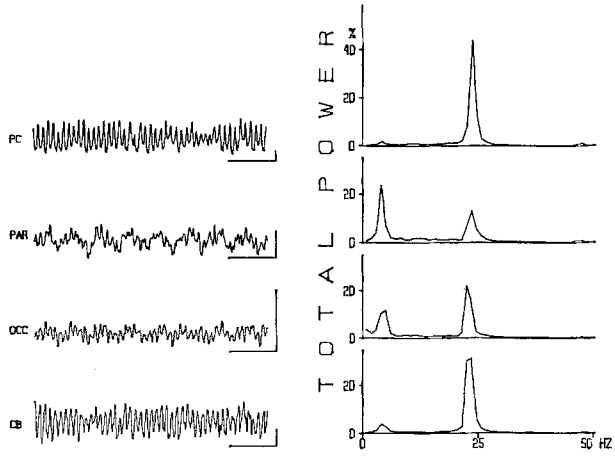

Fig. 1. Tetanus intoxication. EEG of the precentral, parietal, occipital cortical and of the cerebellar lead with the corresponding spectral analysis. Calibration of EEG: 0.4 sec., 50 μV.

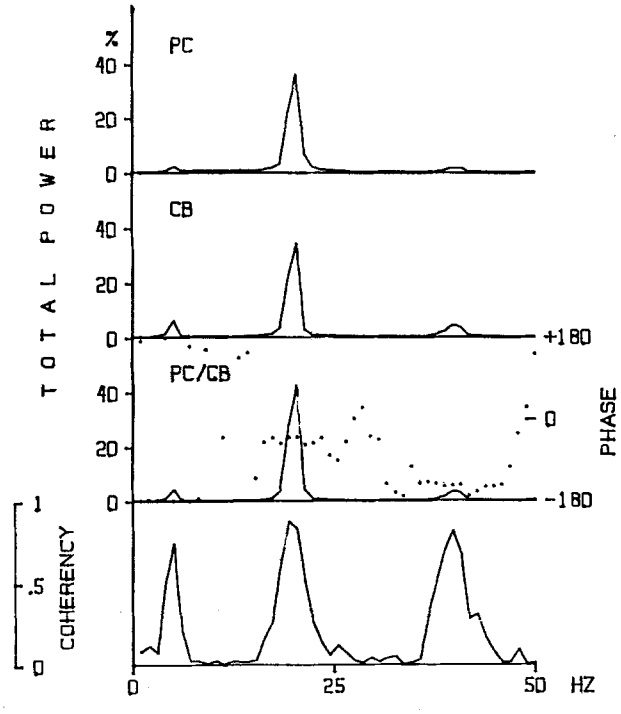

Fig. 2. Tetanus intoxication. Components of spectral analysis of precentral and cerebellar EEG. From top to bottom: Precentral autospectrum, cerebellar autospectrum, precentral and cerebellar crosspectrum and phase (dotted), coherency. The peak at 5 Hz indicates the coherency of hippocampal theta-rhythm, the one at 40 Hz the coherency of the harmonic frequency, which could be observed in many of our experiments.

sively, in average 0.9 Hz/h. The lowest frequency we could find was 11 Hz on 1 animal after 21 h registration. The amplitude (unipolar lead) was found not to exceed 100 μV, usually being between 30 and 50 μV.

The cortical EEG of these animals revealed a rhythmic activity (Figure 1) from the beginning of registration. Not only was the frequency of this ryhthm identical with the above-mentioned cerebellar one, but the coherency was also highly significant (Figure 2). The cortical rhythm was most obvious at the precentral area because of its high amplitude (up to 120 μV) and the less striking theta rhythm in this lead.

In 3 experiments, mid-brain transsection was performed. In all 3 cases, a pattern of EEG at rest resulted instead of the previous cortical rhythmic activity. In one of these experiments, we were able to record regular cerebellar activity following the transsection.

A preliminary evaluation of cortical phase relationship revealed a phase shift only in the anterior-posterior direction with the rhythm being in phase at electrodes placed symmetrically at both hemispheres. The phase relation between cerebellar rhythm and any reference point (in Figure 2 the precentral lead) depends on the depth of the cerebellar electrode, thus indicating phase differences within the cerebellum.

Transition stage. On 3 animals we were able to study the development of cortical and cerebellar rhythmic activity. In a typical experiment, a rabbit was injected with 10^4 LD_{50} tetanus toxin i.v. Surgical procedures were started 18 h later, in the presence of symptoms of reluctance to move and stiffness of gait. At the beginning of registration, only an inconspicuous cerebellar rhythm of 35 Hz was present. It became more regular as the experiment proceeded. The cortical EEG was characterized at the beginning by slow waves and precentral spindles. In the course of a few h, the picture changed to cortical desynchronization, concomitant with continuous hippocampal theta rhythm, and 10 h later the above described rhythm was established.

Local tetanus. Cortical or cerebellar rhythmic activity could not be seen in either brainstem tetanus or in local tetanus of the limbs.

Discussion. Cerebellar rhythmic activity is not specific for tetanus intoxication. It occurs under the influence of 'barbiturate like agents'[5] and strychnine[5–8] and may be induced by arousal stimulation[7,8]. From the latter condition, it can be clearly distinguished by its regularity and the occurence of lower frequencies. As noticed at the transition stage, we never saw a sudden change from less regular to the highly rhythmic cerebellar activity. We may therefore assume that the cerebellar rhythm of tetanus intoxication developes gradually. Our experimental setup does not permit any conclusion as to cause and origin of the cerebellar rhythm. Tetanus toxin may be similar in this respect to strychnine, which is said to induce it by influence on spinal cord and brainstem[6–8], although we were unable to find the cerebellar rhythm in animals with brainstem tetanus.

On the other hand, the rhythmic activity of cortical areas seems to be significant. The toxin, as clearly demonstrated by our mid-brain transsections, does not act directly on cortical structures[9].

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Potentiation of Ethanol Narcosis by Dopamine- and L-DOPA-Based Isoquinolines

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Summary. The isoquinolines, salsolinol and 3-carboxysalsolinol, prolong ethanol-induced narcosis in mice. Pretreatment with carbidopa increases the effect of 3-carboxysalsolinol but not of salsolinol. These results suggest that ethanol sleeping-time potentiation by L-DOPA may involve a partial conversion to the isoquinoline in vivo. A central depressant action of salsolinol or the 3-carboxy analogue is suggested.

Many studies have indicated that neuroamines, or their metabolites, may participate in the narcotic action of ethanol. Several sleeping time studies, in which administrations of ethanol were preceded by injections of dopamine and 5-hydroxytryptamine[2,3] and their precursors, L-DOPA and 5-hydroxytryptophan[4], have shown that these substances significantly prolong the depressant action of the alcohol. Attention has focused, however, on the aberrant reductive pathway metabolites, the arylethanol products, dihydroxyphenylethanol (DOPET) from dopamine and tryptophol and 5-hydroxytryptophol from 5-hydroxytryptamine[3,5]. These metabolites are also able to produce prolongation of ethanol-induced narcosis; yet the results indicate that the neuroamines are more potent potentiators than either the precursors or the reduced metabolites.

Other unusual metabolites may occur under the experimental conditions employed. Acetaldehyde, the prime

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