Neuroleptanalgesia and the Function of the Auditory Cortex in the Cat

Anssi R. A. Sovijärvi, M.D.,* and Kimmo Sainio, M.D.*

Information about the effects of neuroleptanalgesia (NLA) on the electrical function of the auditory cortex was obtained by recording gross electrical and unit activity in the primary auditory cortex of the cat after administration of droperidol and fentanyl (Thalamonal). In the EEG no change could be detected visually after an intramuscular injection of Thalamonal, nor did spectral analyses reveal any significant alteration. Pentobarbital, on the other hand, caused a highly significant slowing of the EEG. Single-cell activity was clearly depressed by pentobarbital, but during NLA most of the functional neurons of the auditory cortex were firing spontaneously and responded readily to various types of sound stimuli. From these findings the authors conclude that NLA at the level of surgical anesthesia does not significantly affect the electrical function of the auditory cortex and the auditory pathway in the cat. (Key words: Auditory cortex; Unit activity; EEG analysis; Neuroleptanalgesia; Pentobarbital.)

NEUROLEPTANALGESIA (NLA), which results from the effects of a neuroleptic drug and a potent narcotic analgesic, is not a state of total unconsciousness like general anesthesia. Nevertheless, the level of analgesia and sedation is adequate for surgical procedures in man1-4 and in animals.5-7 During operations using NLA, however, human patients are able to respond immediately to quiet commands.5,7 This peculiar reactivity to sounds has also been found in dogs.5 From these observations it has been inferred that the functional state of the auditory system is not essentially altered by NLA, but direct neurophysiologic evidence of this has so far been lacking.

The effects of NLA on the cortical EEG have been studied by many authors.5-11 It has usually been found that NLA causes a slight slowing of EEG frequency, which may be only temporary. For instance, in man the normal alpha activity usually returns about 15 minutes after iv injection of the drugs.11 Thus, the depressant effects of NLA on the reticular activating system and the cerebral cortex do not appear to be very strong or permanent, supporting the hypothesis presented above.

We set out to examine whether NLA affects the electrical function of the auditory system at the cortical level, using both gross electrical and unit activity recordings. Apart from its anesthesiologic interest, this work was planned to test the methods used in our study of the functional properties of the neurons of the auditory cortex, which is now in progress.

Material and Methods

Thirty cats, each weighing 1.8 to 4.7 kg, were used in these experiments. Unit activity was recorded from 50 cells of the auditory cortex during 23 acute experiments. Three cats with chronically-implanted electrodes were used for EEG recordings. Four cats served as controls of the experimental situation.

The experiments for unit activity recordings, which lasted 10 to 15 hours, were carried out in a dimly lighted room, the level of background noise being 35 db. The cats were premedicated with atropine (0.1 mg/kg, sc). Five minutes later the drugs for NLA were administered im: fentanyl, 0.025 mg/kg, and droperidol, 0.8 mg/kg (Thalamonal,† 0.35 ml/kg). The adequacy of analgesia was tested by pinching an auricle and the tip of the nose with surgical forceps and observing the withdrawal reaction for pain. The initial dose of fentanyl was insufficient in five cats, and therefore an additional dose of 0.01 mg/kg was given. The subsequent doses of NLA

* Research assistant in Physiology.

Received from the Institute of Physiology, University of Helsinki, Helsinki, Finland. Accepted for publication March 9, 1972. Supported by a grant of the Finnish Cultural Foundation.

† Corresponds to Innovar; Thalamonal and Innovar contain fentanyl and droperidol in the ratios 1:30 and 1:50, respectively.

406
agents were also higher than usual in these five cats (fentanyl, 0.02 mg/kg, and droperidol, 0.5 mg/kg). Generally, additional doses of fentanyl (0.01 mg/kg) were administered every hour and additional doses of droperidol (0.25 mg/kg) every three to four hours. The cats were paralyzed with gallamine triethiodide (Flaxedil), 4 mg/kg, im, with additional doses if needed. Because the levels of analgesia and sedation could not be tested in paralyzed cats, and because there are no data concerning the pharmacology of NLA drugs in the cat, the scale for additional doses was estimated from the results obtained with our four control cats. Artificial respiration with room air was carried out with a Harvard small-animal respirator through an endotracheal tube. The depth of respiration was controlled by continuously measuring the carbon dioxide concentration of the expired air with a carbon dioxide analyzer (Godart Capnograph KK). End-tidal CO₂ values of 3.8 to 4.5 per cent seemed to indicate normoventilation according to Astrup values. Rectal temperature was measured continuously with an electric thermometer and kept within the limits of 36.5-37.5°C with a warmed experimental table and an infrared lamp. ECG was monitored with an oscilloscope. Changes in the QRS complex were rare, and heart rates seemed to remain within normal limits. A saphenous vein was cannulated in almost every animal for infusion of isotonic NaCl solution.

The unit activity recording system was modified from the technique of Hubel. The skull was opened with a drill over the anterior or middle ectosylvian gyrus of the right hemisphere, which is the area in which the primary auditory cortex is located in the cat. Dura mater was not usually removed. A plexiglass cylinder was attached tightly to the skull around the hole. A hydraulic micromanipulator fixed to the cylinder, thus forming a closed chamber, which was filled with Ringer's solution. Action potentials from the cells of the primary auditory cortex were recorded extracellularly with platinum-iridium microelectrodes. The electrode was moved perpendicularly to the surface of the cortex. The depth coordinates were obtained from the scale in the manipulator with reference to the contact point on the cortex. The spikes were amplified (Tektronix 122), filtered for noise (Krohn-Hite 3700 F), monitored with an oscilloscope, and audioamplified for headphones. For stimulation, a wide selection of sound patterns was used. Sounds were played back from a magnetic tape and fed into a loudspeaker situated in front of the cat. Sound pressure levels between 65 and 85 dB (re 0.0002 dynes/cm²) were used. Successful impulse trains, together with the stimulation sounds, were stored on magnetic tape with an eight-channel tape recorder (Precision Instrument, P1-6200). Typical results were photographed from the oscilloscope with a kymograph camera (Grass C 4).

The unit responses were analyzed visually and acoustically with the aid of an oscilloscope, headphones, and films, in which the stimulus and the response are seen simultaneously. Two unit activity experiments were carried out during pentobarbital anesthesia (Nembutal, 35 mg/kg, ip). In these experiments the cats were breathing spontaneously. After the experiments the recording areas were examined macroscopically. Serial sections were prepared for histologic examination to determine the thickness and cytoarchitecture of the cortex at the recording sites.

For EEG recordings, permanent epidural electrodes were implanted in three cats during pentobarbital anesthesia (Nembutal, 35 mg/kg, ip). The electrodes were implanted in the frontal, parietal, occipital, and temporal (anterior and posterior auditory) cortices of the right hemisphere, and in the vertex, which was the reference site. Immediately after implantation, an EEG was recorded to show the effects of pentobarbital. Two to three days later, control measurements of the EEG were carried out, followed by recordings during NLA (droperidol, 0.8 mg/kg, and fentanyl, 0.025 mg/kg, im). During these experiments the cats were lying in a basket and breathing spontaneously. Nine experiments were carried out with these three cats.

EEG's were recorded on paper with an eight-channel Devices M.8 polygraph, using a time constant of 0.1 sec, and stored on magnetic tape with an FM tape recorder (Thermionic Products, T 4000). Artifact-free EEG samples of 50 seconds were then digitized and analyzed off-line with a μ-Linc computer.
The samples for analysis from the EEG during NLA were taken 20 to 25 minutes after injection of the drugs.

Computer analysis of the EEG was performed as described by Putkonen et al.\textsuperscript{16} For the spectral analysis, autocorrelograms were first computed for five successive periods of 10 seconds each, and power spectra were derived from them by Fourier transformation. Furthermore, the relative spectral intensity of each of the frequency bands generally used was calculated as a percentage of the total spectral intensity. The statistical significance of the differences between the frequency bands of the control and the medicated groups was tested with Student’s t test. The mean amplitude level was expressed as the variance of the EEG, and the coefficients of variations were calculated to show the stability of the EEG amplitude.

Results

In most cases, the cats became a little drowsy 10 to 15 minutes after injection of Thalamonal, and no pain reaction could be elicited. Nevertheless, most responded well to various kinds of sound stimuli, turning their heads towards the source of the sound. On two occasions these drugs caused excitement, and the experiments had to be discontinued. During EEG recordings NLA drugs seemed not to depress normal spontaneous respiration.

EEG

On visual analysis of the EEG of the auditory cortex we could not detect any difference between control and NLA recordings, of which examples are shown in figure 1. In both groups periodic alpha activity and slower theta activity were prevalent. During pentobarbital anesthesia, the dominance of delta waves was evident. In the power spectra, which were computed from the EEG recordings of all animals, the spectral variability between successive EEG samples seemed considerable, and was almost the same in the control and the NLA groups, whereas in the pentobarbital group the variability was negligible, as in the example in figure 2. The relative intensities of the spectra in different frequency bands resembled each other in the normal state and during NLA. Closer scrutiny, however, disclosed a minor change to
slower frequencies during NLA. An example of this tendency is evident in table 1, which shows the means and standard deviations of the percentage parts of the frequency bands computed from five 10-second EEG samples of Cat 27. Alpha bands diminished and theta bands increased during NLA, but these changes were not significant in any cat studied. In contrast, in all cats pentobarbital caused highly significant ($P < 0.001$) increases in delta activity and significant ($P < 0.01$) decreases in theta, alpha, and beta activities (table 1).

The mean amplitude, expressed as the variance of the EEG amplitude ($\mu^2$/sec), was not changed during NLA, unlike the mean amplitude during pentobarbital anesthesia (fig. 3). The stability of the amplitude did not change, as indicated by the coefficients of variation. During pentobarbital anesthesia, the EEG amplitude was obviously higher in the auditory cortex than in the other areas examined (see Methods). An example of this is shown in figure 1.

UNIT ACTIVITY

The units of the primary auditory cortex seemed to function without any marked depression during NLA. Of 50 cells, all except two were firing “spontaneously,” which means firing in the experimental circumstances without any noxious stimuli. Five cells did not respond to any kind of sound stimuli but were spontaneously active. Most of the other cells showed good responses, with bursts of spikes or with inhibition in response to various types of sounds. Both pure tones and complex sound patterns were used. Figure 4a indicates a clear excitatory “on” response and a faint “off” response to a tone of 200 cps. In figure 4b the activity of another neuron of the auditory cortex seems to follow immediately the stimulating sound pattern.

In two experiments we recorded unit activity of the auditory cortex during pentobarbital anesthesia. The activity of the cells seemed to be strongly depressed; few active cells could be found, and the responses to sound stimulation were minimal, or there were no responses at all.

Discussion

During NLA the cats were usually a little drowsy, but they responded well to sound stimulation, like human beings \(^3\) and dogs.\(^9\) The neurophysiologic evidence we have obtained also shows that NLA has only minor effects on the function of the auditory cortex.

NLA caused statistically-non-significant slowing in the EEG of the auditory cortex (fig. 2, table 1). This pattern, with a minor increase in the theta band (4-8 cps) resembled that of the drowsy state in the normal EEG of the cat.\(^17\) Nilsson and Ingvar\(^18\) have reported that a combination of fentanyl and droperidol slightly increases EEG frequency and cerebral blood flow in the cat. The difference between their results and ours may have been due to the different modes of administration of the drugs: they injected the drugs iv, which may have resulted in more rapid stimulation of the reticular formation by fentanyl,\(^19\) ex-
TABLE 1. Relative Intensities of the Frequency Bands of the Auditory EEG of Cat 27 in the Control Period, during Neuroleptanalgesia, and after Pentobarbital (Mean ± SE)*

<table>
<thead>
<tr>
<th>Frequency band (cps)</th>
<th>Relative Intensity (Per Cent)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anterior Auditory Cortex</td>
</tr>
<tr>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>Delta, 0-1.56</td>
<td>6.79 ± 2.25</td>
</tr>
<tr>
<td>Delta, 1.57-4.69</td>
<td>22.5 ± 8.83</td>
</tr>
<tr>
<td>Theta, 4.70-7.82</td>
<td>26.5 ± 5.07</td>
</tr>
<tr>
<td>Alpha, 7.83-12.5</td>
<td>25.3 ± 7.38</td>
</tr>
<tr>
<td>Beta1, 12.6-20.3</td>
<td>11.7 ± 0.37</td>
</tr>
<tr>
<td>Beta2, 20.4-32.8</td>
<td>7.02 ± 1.18</td>
</tr>
</tbody>
</table>

* Computed from the percentage means of five 10-second EEG samples. Values during neuroleptanalgesia and after pentobarbital were compared with control values by Student's t test.
† p < 0.001.
‡ p < 0.01.

ceeding the simultaneous depressant effect of droperidol. Most of the earlier studies agree in showing that NLA causes a slight and temporary slowing of the EEG in man and in many animals. No special studies of the EEG of the auditory cortex were reported in these previous papers.

The excitation which occurred in two cats in our series after an injection of the usual dose of Thalamonal was evidently caused by fentanyl, a morphine-like drug.

General anesthetics have a profound depressant effect on the function of the cerebral cortex; they decrease the metabolism and the blood flow in the brain, which is reflected in the typical slowing of the cortical EEG during pentobarbital anesthesia illustrated in figures 1 and 2. For instance, barbiturates and ether effectively depress the spontaneous unit activity and diminish the sensitivity of the cortical cells to peripheral stimuli. It has previously been shown that this is also the case in the auditory cortex, in which general anesthesia decreases the number of functional units and reduces their capacity to respond. This decreased responsiveness in the auditory cortex is partly due to the depressant effects of general anesthetics on the auditory pathway. For instance, ether and pentobarbital may totally block the function of all the auditory relay nuclei. Our results from the unit ac-

![Fig. 3. Variance of EEG amplitude, expressed as µV/sec in different states. Anterior auditory cortex, AUDa; posterior auditory cortex, AUDp.](attachment:image.png)
tivity recordings during pentobarbital anesthesia were uniform with respect to these findings. During NLA, however, the auditory units were clearly more active. The most functional neurons were firing spontaneously and responded readily to various types of sound stimuli, as seen in figure 4. Because, owing to the acute nature of the unit activity experiments, we have no control data, our recordings during NLA have been compared with corresponding recordings obtained from unanesthetized cats in previous studies. The function of the auditory cortex at the single-cell level in the normal state does not seem to differ significantly from the function during NLA with regard to spontaneous activity and responsiveness to sounds. This also shows that under the influence of NLA the subcortical auditory structures are in a functional state which closely resembles normal.

Accordingly, NLA induced by a combination of fentanyl and droperidol in the doses needed for surgical anesthesia does not have a significant effect on the function of the auditory cortex or the auditory pathway in the cat. NLA may, however, cause some changes in the latency times and characteristic frequency-response areas, which were not measured in this study.

In conclusion, NLA appears to be suitable for neurophysiologic studies of the auditory cortex. It may also be useful in ear operations in which local anesthesia cannot be used and hearing must be tested.

The authors appreciate the skillful and unflinching help of Miss Pitti Jussila, M.B., Mr. Kari Koskinen, Mr. Timo Siltanen, M.B., Mr. Reito Sipila, M.B., and Miss Tytti Tolski, M.B., during the time-consuming experiments.

References
5. Love JA: Use of fentanyl and droperidol in guinea pigs, lemmings, ground squirrels and cats. JAVMA 157:675-677, 1970

Drugs and Their Actions

MUSCLE RELAXANTS IN TETANUS The muscle relaxant effects of chlorpromazine (25 mg), phenobarbital (100 mg) and meperidine (300 mg) in cases of tetanus were measured by the use of ventilatory lung function tests. Tidal volume, inspiratory reserve volume, expiratory reserve volume, and vital capacity were measured in 15 patients with tetanus. Readings were made before and one hour after intramuscular administration of the drug. Statistically significant improvement in all variables occurred after the administration of each drug. (Tikare, S. K., and others: Evaluation of Muscle Relaxants in Tetanus, Clin. Pharmacol. Therap. 13: 193-195, 1972.)