Polygraphic Studies on the Effects of Droperidol (Dehydrobenzperidol, R-4749) in Albino Rat

ISAKO HOMMA, YOJI ISHIYAMA and MITURU EBE
Department of Physiology, The Toranomon Hospital, Tokyo

HOMMA, I., ISHIYAMA, Y. and EBE, M. Polygraphic Studies on the Effects of Droperidol (Dehydrobenzperidol, R-4749) in Albino Rat. Tohoku J. exp. Med., 1972, 108 (1), 25-37 — The effects of Droperidol on EEGs of both cortex and hippocampus, VEP, ECG, respiration and body movement were investigated in sixteen adult albino rats. The dose administered, i.p., was graded 0.05, 0.5, 2.5, 5, 25, 50, 75 and 100 mg/kg. EEGs in both cortex and hippocampus were stable apparently in small dose, but the regularity in cortical EEG increased according to the frequency analysis. In large dose both EEGs changed to slow rhythm superimposing fast activity and in extremely large dose they faded out. Peak latencies of the components in VEP shortened in small dose and delayed in large dose. Pulse rate increased in small dose, but decreased in large dose. Ischemic effects to ECG were found in extremely large dose. Respiratory rate was hardly affected. Body movement was calmed down. The maximum effects appeared at 15 to 60 min after the medication and the effects continued for several hours, but they were well correlated with the administered dose.

—Droperidol; neuroleptics; EEG; VEP; ECG

The most desirable effect of anesthetics is to remove pain without loss of consciousness and to be indifferent to the medium in calm. Since 1959, the neuroleptanalgesia established by DeCastro has been taken as the desirable anesthesia (DeCastro and Mundeleer 1962). He used the combination of pheno- peridium and haloperidol for it. In this method the effect of analgesics for pain is enhanced by the neuroleptics, and the autonomic reflex, especially the emetic effect following the analgesics, is suppressed. Recently, Thalamonal which is combined with Fentanyl as analgesics and Droperidol as neuroleptics in ratio of 1 to 50 has been used. Although there are some clinical and physiological reports about the drug (Nilsson and Janssen 1961, Holderness et al. 1963, Dobkin et al. 1964), the neuroleptic effect of Droperidol itself is scarcely known. Especially, the analysis of the effect of Droperidol on the central nervous system is not sufficiently studied.

In this paper, the effects of Droperidol on EEGs in the cortex and the hippocampus, visual evoked potential (VEP), ECG, respiratory rate and body movement in albino rat are presented.

METHODS

Sixteen adult albino rats were used for our experiment. Under ether anesthesia the rat was fixed on the stereotaxic apparatus and the surgical procedure was performed, and then it was kept in a dark room throughout the experiment.

Received for publication, December 7, 1971.
EEG: The skull was drilled for fitting two ball electrodes on the cortex of both area 17 and the occipital area on one side. A needle electrode was stereotaxically inserted to the hippocampus through a drilled hole of the skull on the other side. The atlas by König and Klippel (1963) was referred to the stereotaxic procedure. The cortical and hippocampal EEGs were recorded by an electroencephalograph (Hitachi Co.) together with the other phenomena and taped simultaneously on a data recorder (TEAC R-500). The EEGs in the tapes were analyzed for each five sec with a frequency analyzer of Walter type (San’ei Co.), which has ten band ranges of 0.5 to 1, 2 to 3, 4 to 5, 6 to 7, 8 to 9, 10 to 11, 12 to 13, 14 to 18, 19 to 25 and over 26 Hz.

VEP: VEP was induced by a stimulator of Xenon flash (Nihonkoden Co.) from the cortex of area 17. Flash source was placed at 50 cm in front of the eyes. The intensity was 2.0 Joule. VEPs induced by repeated stimulation were added thirty times with a data processing computer (ATAC 501, Nihonkoden Co.) and consequently average VEP was written out by a X-Y recorder (Yokogawa Co.). The stimulation was repeated at intervals of a few sec. The VEP was taken at intervals of every 5 to 15 min throughout the experiment. Both the amplitude and the peak latency of the component in VEP were measured.

ECG: The needle electrodes were inserted to both forelimbs and the ECG was recorded simultaneously with EEGs. The time constant of the channel was over 1.5 sec. Pulse rate was measured from ECG.

Respiratory rate: It was measured from the oscillatory artifact in the EEG and from the oscillatory rhythm in ECG.

Body movement: It was observed by EMG led from the needle electrodes inserted to the hind limbs and also that led from those of the forelimbs for ECG. It was difficult in real to observe the behavioral body movement, since the material was fastened to the stereotaxic apparatus. However, the artifacts due to the body movement in EEG and ECG were referred to the body movement.

Medication: The chemical structure of Droperidol is shown in Fig. 1. Generally, the effective dose is 0.03 mg/kg and the lethal dose about 77 mg/kg, i.p., in rat. For our experiment the medicated dose was classified into eight grades; 0.05, 0.5, 2.5, 5, 25, 50, 75 and 100 mg/kg. It was administered intraperitoneally after recovering from ether anesthesia for surgical procedure. The rat was dark adapted throughout the experiment.

![Chemical structure of Droperidol](image)

Fig. 1. Chemical structure of Droperidol (Dehydrobenzperidol, R-4749).

RESULTS

EEG: Both cortical and hippocampal EEGs were different in individuals. In cortical EEG the basic rhythm was 4 to 5 Hz and the amplitude was 100 to 200 µV, and in hippocampal one the fast activities were predominant, generally, before the medication. In such a relatively small dose as 0.05 to 5 mg/kg, the basic activities of them did not fluctuate in rhythm and amplitude as those observed before the medication, as shown in Fig. 2. In larger dose, the slow waves of about
3 Hz and the fast waves of about 20 Hz in both EEGs increased, and then the EEG pattern became apparently irregular. As shown in Fig. 3, in such a large dose as 75 mg the slowing of the basic rhythm was enhanced and the amplitude of the fast waves increased in the cortical EEG at 15 min after the medication, while in hippocampal EEG the synchronized slow waves became conspicuous. At 30 min both activities deteriorated and the sharp wave burst sometimes appeared in the hippocampus. However, the fading activities recovered with the lapse of
In the case of 100 mg, as shown in Fig. 4, the activities in both deteriorated soon after the medication. They faded out at 12 min and ECG also disappeared at 17 min.

Although neither cortical nor hippocampal EEGs were changed apparently in small dose, the effect was observed in the cortical EEG by means of the frequency analysis of Walter type analyzer. The results of the frequency analysis in 0.05 and 5 mg were illustrated in Figs. 5 and 6. The ordinates indicated the percentage ratio of each band and the abscissas the time process. Five bands were selected from ten bands in these figures, because in the other five bands the percentage ratio was very small and fluctuated insignificantly in the process. In 0.05 mg, 4 to 5 Hz band increased slightly at first, then decreased and became stable during a few hours, while that of 2 to 3 Hz band declined transiently. In the hippocampal EEG, 4 to 5 Hz band slightly increased initially. In 5 mg, both the initial rise of 4 to 5 Hz band and the initial decline of 2 to 3 Hz band in the cortical EEG were more remarkable, while in the hippocampal EEG each band was stable through the process.

**VEP:** In general, VEP had six components in rat, sequentially named from the 1st to the 6th in order by us. The first component was positive deflection. The peak latency of each component and the amplitude of them were different in individual and the six components did not always appeared all together in every case. The average peak latency of each component will be reported elsewhere by us. The 1st to 3rd components are the early components and the 4th to 6th the later ones.

In Fig. 7, the serial changes of the configuration after the medication in 0.5, 25 and 75 mg were illustrated, respectively. In small dose, the peak latencies in
the early component shortened slightly at first, but later recovered to the former level or slightly delayed, while in the later component they had the tendency to delay and the rhythmic after-discharges were decreased in amplitude (Fig. 7A). In relatively large dose, the peak latencies of the early component were delayed and the amplitudes were decreased slightly with the initial increase. In the later component the amplitude was remarkably decreased and the configuration was deformed (Fig. 7B). In large dose, the peak latencies of both components delayed and the amplitudes of them were unstable, especially in the later component the configuration was variably changed. In Fig. 7C, VEP almost disappeared at 30 min and later recovered again. The change of the amplitude of each component in 0.5, 25 and 75 mg were shown in Fig. 8, in which the abscissa was the time process after the medication. In 0.5 mg, the amplitude was hardly changed with
Fig. 6. Change process of percentage ratio of energy in 5 mg.

Fig. 7. Change of the configuration of VEP after the medication.  
A: 0.5 mg.  B: 25 mg.  C: 75 mg.
Polygraphic Studies on the Effects of Droperidol

Fig. 8. Change of amplitude of each component in VEP after medication. Amplitude was measured from peak to peak. A: 0.5 mg. B: 25 mg. C: 75 mg.

the initial rise (Fig. 8A), but in 25 and 75 mg it decreased more or less (Fig. 8B and 8C). The changes of the peak latencies of the 1st to 3rd in the early component were shown in Fig. 9. In 0.5 mg, they delayed with the initial shortening (Fig. 9A) and in 25 mg they delayed (Fig. 9B), especially in 75 mg at about 30 min they were unmeasurable. In Fig. 10, the percentage increases of the delay of the peak latencies at 15, 30 and 60 min after the medication was summarized concerning the 1st to 4th components. The ordinate indicated the percentage increased and the abscissa the medicated dose. The shortening or delay of the peak latency was well correlated with the dose administered. However, actually
Fig. 9. Change of peak latencies of each component in VEP after medication. A: 0.5 mg. B: 25 mg. C: 75 mg.
in the later component the measurement of both amplitude and peak latency was not accurate, because the configuration was deformed and unstable, especially in large dose.

ECG: Before the medication the pulse rate was individually different from 350 to 510 per min. The change of the pulse rate in each dose after the medication was shown in Fig. 11. In a small dose of 0.05 mg the pulse rate increased at 15 to 30 min after the medication, and it continued for the later process. In 0.5 mg, it increased slightly in initial and gradually decreased lower than the starting level. In 2.5, 5 and 25 mg, it decreased immediately. The more the dose increased, the more the pulse rate decreased, and the longer the effect continued. In 50 and 75 mg, it decreased immediately and remarkably, and in 100 mg it decreased conspicuously and then disappeared at about 17 min, that is, the animal fell to death.
Generally, the change of the pulse rate occurred during 15 to 60 min and the duration of the effect depended on the administered dose. The dependency of the pulse rate on the dose at 15, 30 and 60 min was shown in Fig. 12. The ischemic change of ECG pattern was usually scarce and the rhythmicity was well maintained under the moderate dose. But, in large doses of 50 to 100 mg the ST segment was depressed slightly and sometimes followed arrhythmias.

**Respiration:** The effect of the drug to respiration was very slight, but the tendency to decrease in every dose was observed. In 100 mg, the respiration ceased at 15 min.
Body movement: After the medication the animal was calm and the frequency of the body movement decreased. The indicators of the body movement were both EMG and the artifacts mixed in the polygraphic records and they were illustrated quantitatively in the time process in Fig. 13, in which the amplitude indicated the violence of the body movement. As shown in this figure, the body movement was calmer depending upon the dose.

Fig. 13. Quantitative expression of body movement after administration of each dose. Arrow: injection of the drug.

DISCUSSION

There has been many reports concerning the agents used for neuroleptanalgesia. It is said that the neurolept-analgesics has scarcely any direct effect to the cerebral cortex but suppresses the activity of the reticular system in the brain. That is, it has the sedative effect to the moter and the autonomic reflex, esp. antiemetic effect. It is usually composed of neuroleptics and analgesics, and they enhance their effects on each other. Thalamonal has been recently used as an advanced agent for neuroleptanalgesia, which is composed of Droperidol as neuroleptics and Fentanyl as analgesics in the ratio of 50 to 1. However, the physiological effect of Droperidol is not yet sufficiently analyzed. There have been some reports concerning the effect of Haloperidol which was replaced by Droperidol in neuroleptanalgesics. Ingvar and Nilsson (1961) reported that alpha rhythm in EEG was not influenced by Haloperidol in human. According to Monti (1968), sleep EEG pattern was not effected by a small dose of it in monkey, but in large dose the first period of REM pattern delayed and the duration of the slow wave pattern was prolonged. Droperidol with Phenoperidin, by Bakrer et al. (1968), could not change the cerebral blood flow and in the frequency analysis of EEG the increase of theta band with the decrease of alpha band was induced. However, the effect of Droperidol itself on EEG has not yet been reported in detail by
anyone. In our experiment the EEG patterns on both the cortex and the hippocampus did not change apparently in small dose, but they had the tendency to change to the slow patterns with the fast activity in the large dose. The effect of Droperidol was different between the cortex and the hippocampus in the results of the frequency analysis, that is, the EEG on hippocampus was more stable than that on cortex.

Concerning VEP, the change of the peak latencies in the early component were well correlated with the administered dose, but less dependable in the later component, because the later component was unstable in the configuration. It seems that the shortening of the peak latencies is due to the release from the inhibition on the synaptic transmission of optic pathway in small dose and that the delay of them is due to the narcotic effect of the drug in large dose. The unstability of the later component probably is due to the effect on the reticular formation in brain stem.

According to Yelnosky et al. (1964) and Schaper et al. (1963) Droperidol increased the cardiac output, the cardiac muscle contraction and the pulse rate slightly, and decreased the blood pressure slightly, in dog. They mentioned that these phenomena were caused by the reduction of the peripheral resistance in the total vessels. In our experiment, the pulse rate increased in a small dose and decreased in a large dose. It will be due to the sympathetic effect of the drug. It has been reported that Droperidol has an anti-arrhythmic effect (Yelnosky et al. 1964). In our experiment the arrhythmia was scarcely observed and the change of ST-T was slight, even in the case of large dose. For respiration, Droperidol was less effective in small dose, and in large dose the efficiency of both ventilation and oxygen supply increased, according to Yelnosky et al. (1964) and Schaper et al. (1963). In our experiment the respiratory rate was stable in most cases. It was evident from our experiment that the rats were calmed down even in small dose.

Conclusively, the results of our experiment suggest that the administration of Droperidol in a small dose under 0.5 mg will induce the neuroleptic effect without the provocation of autonomic reflex.

References
Polygraphic Studies on the Effects of Droperidol


