Roles of Cholinergic, Dopaminergic, Noradrenergic, Serotonergic and GABAergic Systems in Changes of the EEG Power Spectra and Behavioral States in Rabbits

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Accepted March 2, 1988

Abstract—In the present study, the influences of cholinergic (ACh), dopaminergic (DA), noradrenergic, serotonergic and γ-aminobutyric acid (GABA) ergic system activation and blocking agents on the cortical (CT) and hippocampal (HC) EEG power spectra were investigated in rabbits. The AChergic agents, physostigmine and atropine, produced marked increases or decreases in peak powers, the changes of which were inversely related to each other, but similar to those of the normal behavioral states. The other agents did not always produce changes. ACh seems to play an important role in the regulation of peak powers. Apomorphine shifted the theta wave peak to higher frequencies and haloperidol shifted it to lower frequencies. The other drugs did not cause a shift. DA seems to regulate peak frequency. These findings suggest that ACh is important for the regulation of consciousness between the wakefulness and SWS states and suggest that DA is involved in the production of REM sleep.

Since the EEG changes in relation to the level of consciousness, EEG signals are very useful for studying brain function. Power spectral analysis can transform the EEG signals into a spectrum [ordinate: power (μV²), abscissa: frequency (Hz)]. The power spectral analysis of EEG signals is different from their visual assessment, most likely because the amplitude of the EEG signal is more important for power spectral analysis than the appearance time, i.e., the power is the square of the amplitude. It has been found that the cortical and hippocampal EEG power spectra each have characteristic peaks, and that the peak power or frequency increases or decreases depending on the level of consciousness (1). Furthermore, the EEG power spectra after administration of drugs acting on the CNS were different from those obtained during normal behavioral states (1). These results suggest that the EEG power spectra can accurately reflect subtle changes in the CNS.

The level of consciousness is considered to be controlled by the balance between the activation and inhibitory systems of the CNS, and that the choline (ACh), dopamine (DA), noradrenaline (NA), serotonin (5-HT) and γ-aminobutyric acid (GABA) ergic systems play important roles in their regulation (2-4). However, the role of each of these systems in the regulation is not clear. It may be possible to obtain more information about the regulation by studying the changes in the EEG power spectra.

In the present study, the influences of ACh, DA, NA, 5-HT and GABAergic system activation and blocking agents on the EEG power spectra of rabbit cortex (CT) and hippocampus (HC) were examined, and the roles of these systems were investigated.

Materials and Methods

Animals and surgical procedure: Thirty male Japanese White rabbits weighing 2.5–3.8 kg were used. The animals were anesthetized with pentobarbital sodium (30 mg/kg, i.v.), and bipolar stainless steel wire electrodes (0.25 mm diameter, insulated except for the last 0.5 mm of the tips; polar
distance, 0.5–1.0 mm) were chronically implanted into the HC (A:–4, L:4, H:5) according to the brain atlas of Sawyer et al. (5). Two stainless screw electrodes (1.0 mm diameter, silver-plated) were placed subdurally at an interval of 2–3 mm on the surface of the CT (A:2, L:2). Each electrode was fixed with dental cement to a perforated hole in the skull and soldered to a connector socket. The socket itself was fixed by means of the cement together with the screws driven into the skull, and all exposed parts of the electrodes were also covered with the cement. For intraventricular injection, some animals were chronically implanted with canulas (guide cannula 23G, injection cannula 21G) in the cerebroventricle (A:0, L:3, H:6). The guide cannula was fixed with cement to the skull. Animals were allowed at least a 1 week recovery period before commencing the experiments.

**EEG recording and analysis:** The animals were moved in a transparent plastic box (26×42×34 cm) which was placed in a sound-proof, shielded room. The EEGs of the CT and HC were recorded bipolarly on a polygraph (Nihondenki San-ei, 361), at a time constant of 0.1 sec and a low pass filter setting of 25 Hz, concomitantly with observing their behavior under unanesthetized and unrestrained conditions. While recording the EEG, power spectral analysis of the EEGs was performed simultaneously for 15 min with a signal processor (Nihondenki San-ei, 7T07), followed by Fast Fourier Transformation at frequencies from zero to 25 Hz. The spectra were plotted on an X-Y recorder as histograms at intervals of 0.22 Hz.

Significant differences for measurements before and after administration were tested using the paired t-test.

**Drugs:** The drugs used in the experiment were aminoxy acetic acid (Sigma), apomorphine hydrochloride (Sigma), atropine sulfate (Wako Pure Chem.), cyproheptadine hydrochloride (Nakarai Chem.), haloperidol (Dainippon Pharm.), L-5-hydroxytryptophan (Sigma), L-noradrenaline bitartrate (Wako Pure Chem.), pentobarbital sodium (Pitman-Moore), phentolamine (Takeda Pharm.), physostigmine sulfate (Wako Pure Chem.) and picrotoxin (Wako Pure Chem.). All drugs were dissolved in saline. For intravenous administration, the drugs were injected into the ear vein. For intraventricular administration, the drugs were injected (0.1 ml/head/min) into the cerebroventricle via a cannula.

**Results**

**EEG power spectra during normal behavioral states**

The CT and HC EEGs and EEG power spectra during normal behavioral states: wakefulness, rest, slow wave sleep (SWS) and rapid eye movement (REM) sleep are shown in Fig. 1. The peak power of the delta waves of the CT and HC increased in the following order: wakefulness or REM sleep, rest and SWS, while the peak power of the HC theta wave increased in the following order: SWS, rest and wakefulness or REM sleep. The peak frequency during the REM sleep state was shifted to a higher value than that during the wakefulness state.

**EEG power spectra after drug administration**

The EEG power spectra of the CT and HC after drug administration at each dose were examined in 2–4 rabbits, and their peak powers and frequencies were compared with those during the wakefulness state and SWS before administration. Animals were allowed at least a 1 week washout period after drug administration, and the same drug was never administered to one animal more than once.

1. **Cholinergic drugs**

1.1. **Physostigmine:** Physostigmine at doses of 0.05, 0.1 and 0.2 mg/kg, i.v., dose-dependently decreased the delta wave peaks and total power in the CT, and it increased the theta wave peaks in the HC. During the 0–45 min period after administration of a dose of 0.2 mg/kg, the CT and HC delta wave peaks were markedly decreased, and the peaks were significantly lower than those for the wakefulness state. Also, the theta wave peaks were significantly higher than those observed for the wakefulness state (Fig. 2, Table 1).

1.2. **Atropine:** Atropine at doses of 2, 5 and 8 mg/kg, i.v., increased the CT and HC delta wave peaks. At a dose of 5 mg/kg, the delta wave peaks during the 0–60 min period after administration were significantly higher than
those for the SWS state. However, at the higher dose of 8 mg/kg, the height of the peak was almost equal to that at the dose of 5 mg/kg (Fig. 2, Table 1). The animals did not show sedation or sleep, and dissociation between behavior and EEG was observed.

2. Dopaminergic drugs

2.1. Apomorphine: Apomorphine at a dose of 0.5 mg/kg, i.v., tended to decrease the CT and HC delta wave peaks and increase the HC theta wave peak. At doses of 1.0 and 2.0 mg/kg, i.v., these phenomena were clear and marked, and the CT delta wave peaks during the 0–30 min period after administration were significantly lower than those observed during the wakefulness state. In addition, the theta wave peaks were shifted to significantly higher frequencies than those for the wakefulness state (Fig. 3, Table 1). The animals did exhibit cage biting and licking.

2.2. Haloperidol: Haloperidol at a dose of 0.5 mg/kg, i.v., tended to increase the CT
delta wave peak. At doses of 1.0 and 2.0 mg/kg, i.v., the CT delta wave peaks increased, but the increases were not marked, and the peaks were lower than those for the SWS state. At the same doses, the HC delta wave peak decreased and the theta wave peak increased, but the theta wave peak was sharp and was shifted to significantly lower frequencies compared with before treatment (Fig. 3, Table 1).

Fig. 2. The effects of physostigmine and atropine on the power spectra of cortical and hippocampal EEGs in rabbits. SWS, slow wave sleep.

3. Noradrenergic drugs

When noradrenaline or phentolamine were administered intravenously, it was difficult to obtain stable EEG recordings, probably because the drugs influenced the heart and blood pressure. Therefore, the drugs were administered intracerebroventricularly in order to obtain stable EEG recordings.

3.1. Noradrenaline: Noradrenaline at doses of 10, 50 and 100 μg/head increased the CT and HC delta wave peaks in a dose-dependent manner. At a dose of 100 μg/head, the delta wave peaks tended to be slightly higher than those for the SWS state (Fig. 4). The animals were sedated.

3.2. Phentolamine: Phentolamine at doses of 50, 100 and 200 μg/head decreased the CT and HC delta wave peaks and increased the theta wave peaks in a dose-dependent manner. At a dose of 200 μg/head, the CT delta wave peaks during the 15–60 min period after administration were significantly lower than those observed during the wakefulness state. The theta wave peaks tended to be slightly higher than those for the wakefulness state; however, the peaks were sharp (Fig. 4, Table 1).

4. Serotonergic drugs

4.1. 5-Hydroxytryptophan (5-HTP): 5-Hydroxytryptophan at doses of 10 and 20 mg/kg, i.v., produced a dose-dependent decrease in the CT and HC delta wave peaks as well as decreasing the theta wave peaks. At a dose of 20 mg/kg, the CT delta wave peaks during the 15–45 min period after administration were significantly lower than those observed during the wakefulness state. The total power of the HC was found to have decreased when compared with the values before treatment. At a dose of 30 mg/kg, i.v., the total power of the HC decreased markedly during the 0–60 min period after adminis-
tration; however, the CT spectra could not be recorded in a stable fashion after 15 min (Fig. 5, Table 1). The animals were aroused and showed tachypnoea.

4.2. Cyproheptadine: Cyproheptadine at doses of 2, 5 and 10 mg/kg, i.v., produced dose-dependent increases in the CT and HC delta wave peaks. At a dose of 10 mg/kg, the heights of the delta wave peaks during the 0–60 min period after administration were similar to those for the SWS state, but the theta wave peaks did not decrease markedly (Fig. 5).

| Drugs                  | Cortex delta wave peak power (μV²) | Cortex delta wave peak frequency (Hz) | Hippocampus theta wave peak power (μV²) | Hippocampus theta wave peak frequency (Hz) |
|------------------------|----------------------------------|--------------------------------------|----------------------------------------|-------------------------------------------|
| Physostigmine (0.2 mg/kg, i.v.) | W) 4.93±0.46                     | 5.13±0.70                            | 17.69±1.78                             | 6.08±0.35                                 |
|                        | S) 3.71±0.60*                     | 0.81±0.22***                         | 36.92±5.78***                          | 6.14±0.26*                                |
| Atropine (5.0 mg/kg, i.v.)  | 21.47±2.93                       | 21.60±3.06*                          |                                        |                                           |
| Apomorphine (2.0 mg/kg, i.v.) | W) 4.52±0.51                     | 5.13±0.91                            | 15.93±1.26                             | 5.60±0.46                                 |
|                        | S) 2.90±0.46**                    | 3.17±1.15*                           | 18.28±1.95                             | 7.56±0.70*                                |
| Haloperidol (2.0 mg/kg, i.v.) | W) 4.32±0.54                     | 4.93±0.90                            | 16.67±2.16                             | 5.87±0.26                                 |
|                        | S) 9.11±0.71***                   | 4.59±1.46                            | 18.56±4.76                             | 4.93±0.14**                               |
| Noradrenaline (100 μg, i.c.v.) | S) 14.31±0.79                     | 18.16±1.25                           |                                        |                                           |
|                        | 15.32±1.99                       | 17.28±1.17                           |                                        |                                           |
| Phentolamine (200 μg, i.c.v.) | W) 5.27±1.00                     | 4.93±0.89                            | 14.85±1.43                             | 6.08±0.16                                 |
|                        | 3.85±1.19*                       | 3.31±1.04                            | 17.14±2.03                             | 5.81±0.35                                 |
| 5-HTP (20 mg/kg, i.v.)  | W) 4.79±0.46                     | 2.43±0.79**                          |                                        |                                           |
|                        | 2.43±0.79**                      |                                        |                                        |                                           |
| Cyproheptadine (10 mg/kg, i.v.) | S) 15.19±1.53                     | 15.73±0.81                           |                                        |                                           |
|                        | 16.13±1.99                       | 15.66±1.80                           |                                        |                                           |
| AOAA (20 mg/kg, i.v.)   | S) 13.23±1.51                     | 14.18±1.74                           |                                        |                                           |
|                        | 22.21±4.96*                      | 21.06±3.38*                          |                                        |                                           |
| Picrotoxin (1.0 mg/kg, i.v.) | W) 4.72±0.84                     | 4.05±0.91                            | 16.24±2.48                             | 5.74±0.41                                 |
|                        | 5.87±0.74*                       | 3.44±1.11                            | 17.01±2.19                             | 5.64±0.27                                 |

The peak power and peak frequency for individual spectra after drug administration were compared with those during the wakefulness or slow wave sleep states before administration, and the significant difference was tested by means of the paired t-test. The peak power values (μV², mean±S.D., n=4) represent relative values, and the peak frequency values (Hz, mean±S.D., n=4) represent real values. The values of μV² and Hz after administration were derived from the spectra which were the most markedly changed. W), wakefulness state before administration; S), slow wave sleep state before administration; 5-HTP, 5-hydroxytryptophan; AOAA, aminoxy acetic acid; *P<0.05, **P<0.01, ***P<0.001.

5. GABAergic drugs
5.1. Aminoxy acetic acid (AOAA): AOAA at a dose of 10 mg/kg, i.v., produced no significant changes in the CT or HC spectra. At a dose of 20 mg/kg, i.v., the CT and HC delta wave peaks increased markedly during the 75–105 min period after administration, and the peak heights were significantly higher than those for the SWS state. At a dose of 40 mg/kg, i.v., the delta wave peaks increased markedly during the 120–150 min period after administration (Fig. 6, Table 1). The animals showed sedation and muscle
Fig. 3. Effects of apomorphine and haloperidol on the power spectra of cortical and hippocampal EEGs in rabbits. The numbers in parentheses are the peak frequencies of the theta waves of hippocampal EEGs.

Fig. 4. Effects of noradrenaline and phentolamine on the power spectra of cortical and hippocampal EEGs in rabbits. i.c.v., intracerebroventricular.

5.2. Picrotoxin: Picrotoxin at a dose of 0.2 mg/kg, i.v., produced no significant changes in the CT or HC spectra. At doses of 0.5 and 1.0 mg/kg, i.v., the CT delta wave peaks decreased for 60 min, but they were still
Fig. 5. Effects of 5-hydroxytryptophan (5-HTP) and cyproheptadine on the power spectra of cortical and hippocampal EEGs in rabbits.

Fig. 6. Effects of aminooxy acetic acid (AOAA) and picrotoxin on the power spectra of cortical and hippocampal EEGs in rabbits.
slightly higher than those recorded during the wakefulness state. The HC delta wave peaks decreased and the HC theta wave peaks increased, but they were as sharp as those observed during the wakefulness state (Fig. 6).

Discussion

The CT and HC EEG power spectra produced after drug administration were compared with the spectra before administration with regard to peak power of the delta and theta waves and the theta wave peak frequency. The effects of ACh, DA, NA, 5-HT and GABAergic system activation and blocking agents on the CT and HC spectra in rabbits are shown in Fig. 7. The peak power of the CT and HC delta waves were decreased by physostigmine, apomorphine, phentolamine, 5-HTP and picrotoxin. They were increased by atropine, noradrenaline, cyproheptadine, AOAA and haloperidol, but the latter did not produce a marked increase. The peak power of the HC theta wave was increased by physostigmine, apomorphine, haloperidol, phentolamine and picrotoxin, while it was decreased by atropine, noradrenaline, 5-HTP, cyproheptadine and AOAA. The ACh system activation and blocking agents, physostigmine and atropine, produced a marked increase or decrease in each peak power, and the changes caused by the two drugs were diurnally opposed to each other, but similar to those during the normal behavioral states. On the other hand, the DA, NA, 5-HT and GABA system activation and blocking agents did not always produce opposite spectral changes, as evidenced by the fact that the spectra after administration of some of the agents were different from the spectra during the normal behavioral states. The DA system activation and blocking agents, apomorphine and haloperidol, respectively, increased the peak power of the theta wave, while the 5-HT system activation and blocking agents, 5-HTP and cyproheptadine, decreased it. The theta wave peaks after administration of the NA and GABA receptor blockers, phentolamine and picrotoxin, were sharp compared to those during the wakefulness state. From these results, it is suggested that the peak power of delta and theta waves of the CT and HC are more or less regulated by all five systems, but ACh plays the most important role in the regulation of the peak powers. The HC theta wave peak was shifted to higher frequencies by the DA receptor activator apomorphine and shifted to lower frequencies by the DA receptor blocker haloperidol. ACh, NA, 5-HT and GABAergic drugs did not shift the peak. Therefore, DA
seems to regulate the peak frequency of the theta wave.
The alterations in the CT and HC EEG spectra during the normal behavioral states and the roles of ACh, DA, NA, 5-HT and GABA systems on the spectra are shown in

Table 2. Alterations in the cortical and hippocampal EEG power spectra in rabbits during the normal behavioral states and after administration of the cholinergic, dopaminergic, noradrenergic, serotonergic and GABAergic system activation and blocking agents

|                        | Cortex |  | Hippocampus |
|------------------------|--------|  |-------------|
|                        | peak power |  | peak power |
|                        | delta wave |  | delta wave | theta wave | theta wave |
| Normal behavioral state|        |  |            |            |            |
| Wakefulness            | ↓      |  | ↓          | ↑          | —           |
| Rest                   | —      |  | —          | —          | —           |
| Slow wave sleep        | ↑      |  | ↑          | ↓          | —           |
| REM sleep              | ↓      |  | ↓          | ↑          | —           |
| Cholinergic system     |        |  |            |            |            |
| Physostigmine          | ↓      |  | ↓          | ↑          | —           |
| Atropine               | ↑      |  | ↑          | ↓          | —           |
| Dopaminergic system    |        |  |            |            |            |
| Apomorphine            | ↓      |  | ↓          | ↑          | —           |
| Haloperidol            | ↑      |  | ↑          | —          | ◄           |
| Noradrenergic system   |        |  |            |            |            |
| Noradrenaline          | ↑      |  | ↑          | ↓          | —           |
| Phentolamine           | ↓      |  | ↓          | ↑          | —           |
| Serotonergic system    |        |  |            |            |            |
| 5-Hydroxytryptophan    | ↓      |  | ↓          | ↓          | —           |
| Cyproheptadine         | ↑      |  | ↑          | —          | —           |
| GABAergic system       |        |  |            |            |            |
| AOAA                   | ↑      |  | ↑          | ↓          | —           |
| Picrotoxin             | ↓      |  | ↓          | ↑          | —           |

Peak powers and frequency were compared with those during the rest state (—). ↑, increase; ↑↑, marked increase; ↓, decrease; ↓↓, marked decrease; ▸, shift to higher frequency; ◄, shift to lower frequency; —, no change.

Fig. 8. Effects of acetylcholine, dopamine, noradrenaline, serotonin and GABA on cortical and hippocampal EEG power spectra in rabbits.
Table 2 and Fig. 8. The peak powers of the CT and HC delta waves decreased during the wakefulness state and increased during the SWS state. The HC theta wave increased during the wakefulness state and decreased during the SWS state, and the peak frequency of the latter was shifted to a higher value during the REM sleep state. When compared to the normal changes of the spectra, brain ACh, DA and 5-HT are believed to activate the CNS, while NA and GABA are considered to be suppressive. However, the spectral changes produced by the ACh, DA and 5-HT system activation agents were not same. The three drugs produced a marked decrease in the CT delta wave power, but the HC spectral changes caused by the three drugs were different, i.e., the theta wave peak was markedly increased by physostigmine, shifted by apomorphine and decreased by 5-HTP. Activation of the ACh, DA and 5-HT systems seem to cause actions which are different qualitatively. ACh has been reported to produce psychological activations which reverse or ameliorate cognitive impairment (6, 7). It is known that apomorphine produces hyperactivity and stereotyped behaviors (8, 9), while 5-HTP produces the abnormal behavior head-twitching (10–12). The differences in the HC spectra caused by the three drugs may be related to the different behaviors caused by the drugs. At any rate, the change in the theta wave peak seems to be important for investigating the activation state of the brain, however, it is difficult to judge that in the brain using only the CT EEG spectra.

Similarly, the relative changes between the CT and HC spectra also seem to be important. Haloperidol and 5-HTP produced abnormal spectral changes, i.e., the changes in CT and HC appeared dissociated when compared to the normal changes. As described above, the HC theta wave peak increases when the CT delta wave peak decreases during the normal behavioral state. While haloperidol increased the theta wave peak but did not decrease the delta wave peak, 5-HTP decreased both the delta and theta wave peaks. These results suggest that the controlling mechanisms for the CT and HC are different. Tokizane (13) reported that the neocortex was regulated by two control systems, one in the reticular formation and one in the hypothalamus, and that the limbic cortex was regulated only by the hypothalamic control system. The present results support the hypothesis that the control mechanisms of the neocortex and limbic cortex are different, and that brain DA and 5-HT may play some role in the differences between the control mechanisms for the CT and HC.

The activation state of the brain, the level of consciousness and the sleep-wakefulness cycle are regulated by the balance between the activation and inhibitory systems of the CNS. The actions of neurotransmitters in the regulation are considered to be important. Amines have been found to play an important role in the regulation, but their actions are not fully understood. The NA locus coeruleus has been reported to be involved in the ascending reticular activating system (14–17). However, data contrary to this hypothesis has been reported (18). Fuxe et al. (19) reported that clonidine, an α-receptor stimulator, increased the sleep state. Furoxan, an α-receptor blocker, increased the state of wakefulness. The results of the present study are similar to their results in that they indicate that NA may play an inhibitory role in the CNS. Jouvet et al. (20–22) reported that 5-HT applied to the raphe nuclei produced sleep. However, the exact relationship between 5-HT and sleep is not clear (23, 24). It has been reported that quipazine, a 5-HT receptor agonist, produced suppression of SWS and that methysergide, a 5-HT receptor antagonist, blocked the suppression (25, 26), while 5-HTP was found to increase the degree of wakefulness in rats (27). The findings of the present study are similar to these results and indicate that 5-HT plays an activating role in the CNS. This hypothesis is contrary to that of Jouvet et al. (20–22). DA has been reported to promote REM sleep (28, 29). As described above, apomorphine produced a shift in the theta wave peak, a phenomenon which is characteristic of a spectral change during REM sleep. The present data, therefore, also support the hypothesis. However, it has also been reported that the promotion of REM sleep is controlled by ACh (30–32) or NA (20–22). Thus it appears that amines certainly do play
an important role in the regulation of the activation and inhibitory systems, and their actions are different from a qualitative standpoint.

On the other hand, it has been reported that brain ACh is important for regulation of the arousal state (2-4) and that amines are considered to be modulators or regulators of ACh transmission (33, 34). The present results also suggest that ACh plays an important role in regulating the level of consciousness because ACh played an important role in the changes of the CT and HC EEG spectra. However, unlike DA, ACh could not shift the theta wave peak. Furthermore, blocking the ACh system did not produce behavioral sleep, i.e., atropine produced dissociation between behavior and the EEG. Therefore, ACh seems to be limited to controlling the level of consciousness. As described above, ACh has an activating effect on the CNS, while NA is suppressive. ACh and NA are transmitters of the parasympathetic and sympathetic nervous systems, respectively. A difference in the mechanisms between the peripheral and central nervous systems may be involved in the dissociation, although it is difficult to draw any definite conclusions. Though ACh may not control all consciousness, the present data indicate that the role of ACh is more important than the other neurotransmitters.

From these findings, it may be concluded that ACh is important for the fundamental changes which occur between the wakefulness and SWS states, and that DA, NA, 5-HT and GABA play roles in the regulation of the delicate changes in consciousness, such as the role of DA in the production of REM sleep.

Acknowledgments: The author wishes to thank Professor Dr. S. Ueki and Dr. S. Watanabe, Department of Pharmacology, Faculty of Pharmaceutical Sciences, Kyushu University, for helpful advice.

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