Cerebral Circulation, Metabolism, and Electrical Activity during Convulsion Induced by Megimide

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There have been many works on cerebral electrical activity (EEG) during convulsion, however, very few on cerebral blood flow (CBF) because of lack of adequate method for CBF during convulsion. Since CBF is influenced by blood pressure and vascular resistance which is greatly influenced by metabolic activity, measurement of metabolic activity should simultaneously be made. Method of continuous recording of CBF by thermistor, of metabolic activity by PO₂, PCO₂, pH, and Na⁺ have been developed in our laboratory and these methods were applied to the study of convulsion induced by Megimide.

Correlation between the electrical activity of the cortex and the cerebral blood flow has been investigated by Gibbs⁶, Gibbs et al.², Schmidt and Hendrix⁹, Jasper and Erickson⁴, Darrow et al.⁸, and Ingvar⁶. There have been several methods for measuring the cerebral blood flow such as Kety and Schmidt⁷,⁸, Lassen and Munck⁹, Nylin and Blömer¹⁰. However, for a further study of the correlation between the cerebral blood flow and the electrical activity a continuous recording of cerebral blood flow with sufficient accuracy is necessary and the following methods have been used; the Thermostrohmuhr of Reif¹⁵, heated thermocouples¹₂,¹₃, photoelectrical methods¹⁴, "Cranial Window" technique¹⁰, and direct measuring of blood drops¹⁶,¹⁷,¹₈,¹⁹,²₀. Indeed, a study of this correlation is interesting, but a further detailed investigation cannot be made without the concurrent measuring of metabolic activity of the brain, because cerebral blood flow is influenced by both blood pressure and cerebrovascular resistance, and the latter is greatly influenced by carbon dioxide tension which is produced by metabolic activity. Recently new techniques have been developed for concurrent and continuous recording of cerebral blood flow, brain oxygen tension (PO₂), pH, sodium ionic activity (Na⁺), blood pressure and EEG in our laboratory in collaboration with Dr. Meyer in Detroit.

The paper presented here will show the effect of Megimide on cerebral circulation, metabolism and electrical activity in cats.

Method and Materials

Cats weighing 3–3.5kg were used. The animals were anesthetized with ether and all operative procedures were performed under general anesthesia. After exposure of the right femoral vein and artery, polyethylene catheters were inserted and the arterial catheter was connected to an electric manometer (Nihon Koden, MP-3) for continuous recording of blood pressure and the venous catheter was used for injection of drugs. Tracheostomy was routinely performed and tracheal cannula was connected to the respirator immediately after immobilization was made with d-tubocurarine (Amelizol) intravenously. After the cat was fastened to a head holder, craniectomy was performed over one hemisphere and dura was carefully removed. Then electrodes for recording PO₂, PCO₂, pH, sodium ionic activity and ther-

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Japanese Circulation Journal Vol. 29 May 1965 449
mistor were placed on the pial surface of the exposed brain. Thermistor was used for measuring the local cortical blood flow. The principle and characteristics of each electrode were previously reported in detail[21,22,23,24]. Electroencephalogram was recorded from two platinum wires placed on either side of the electrodes for measurement of cortical blood flow and metabolism. The data were recorded by means of 8 channel and 2 channel inkwriting polygraphs. Records of blood flow and metabolism were made at slow speed (10–30 mm/min) and electroencephalographic records were made at conventional speed (30 mm/sec). An inhalation of 10 per cent carbon dioxide in oxygen through the tracheal cannula was routinely performed so that the reactivity of both animal and each electrode could be ascertained.

RESULTS

Figure 1 showed the effect of Megimide 5mg/kg administered intravenously into cat. Cerebral blood flow, PO₂ and PCO₂ increased, pH and Na⁺ decreased, blood pressure increased and EEG showed the seizure pattern. Typical seizure pattern in the EEG induced by Megimide was shown in Fig. 2: 'A' demonstrated the control recording before the administration of Megimide, 'B' was the recording during the ad-

| Table I Summary of the Effect of Megimide on Cerebral Circulation, Metabolism and EEG in Cat |
|-----------------|-----------------|-----------------|-----------------|
| T               | PO₂             | PCO₂            | pH              | Na⁺            | BP             | EEG            |
| increased       | 11              | 11              | 7               | 3              | 1              | 9              | 11             |
| decreased       | 0               | 0               | 0               | 7              | 8              | 0              | 0              |
| no change       | 0               | 0               | 0               | 0              | 2              | 0              | 0              |
| No. of exp. trend | ↑               | ↑               | ↓               | ↓              | ↑              | ↑              | ↑              |
| p-value         | <0.001          | <0.001          | <0.01           | <0.05          | <0.05          | <0.001         |

Fig. 1. Effects of Megimide (5mg/kg) on cerebral circulation, metabolism, and EEG in normal cat.

*Japanese Circulation Journal* Vol. 29 May 1965
ministration, 'C' showed the beginning phase of seizure, 'D' was the typical tonic seizure, 'E' the clonic seizure, and 'F' showed the flat. Then EEG recovered to normal in 'G' and 'H'. Table I showed the summary of effect of Megimide. Changes of all parameters except for pH were statistically significant. The drug caused spike activity or marked activation to appear in the EEG in all experiments. During the seizure blood pressure and cerebral blood flow increased. However, cerebral blood flow usually increased before the increase in blood pressure had remained increased at the end of the seizure after the blood pressure and returned to normal levels. PO₂ increased corresponding to the increased blood flow, however, in 2 cases the increase in PO₂ was followed by decrease probably due to the increase in oxygen consumption. PCO₂ increased and pH tended to decrease. Decrease in sodium ion activity was corresponded to the seizure in the EEG as seen in Fig. 1.

COMMENT

Megimide (ββ'-methyleneyl glutarimide) was first reported as a barbiturate antagonist by Shaw et al. [2], and later it was found that there was no direct antagonism in a proper sense between Megimide and barbiturates. Megimide was used as an activating agent in clinical electroencephalography first in Europe [20]. And it was said that effects of Megimide closely resembled those of pentylentetrazol on the cerebral blood flow [27] as well as on the electrical activity of the brain [26, 25], that is, the increase in cerebral blood flow and seizure activity in the EEG were observed. But Megimide had a better tolerance and more gentle action, and the clinical application of Megimide was safer than that of pentylentetrazol [28], because Megimide had the less disagreeable side effects and the safety margin of Megimide between the activating and the convulsive dose was larger than that of pentylentetrazol. The strength of an excitatory action of Megimide varies from structure to structure and from animal to animal, so the definite convulsive dose of Megimide cannot be decided uniformly to every animal. In our experiments, more than 5 mg/kg of Megimide was administered and in all experiments spike

Fig. 2. Effect of Megimide on EEG. This figure shows the seizure activity.

Japanese Circulation Journal Vol. 29 May 1965
activity or marked activation in the EEG was observed. The increase in cerebral blood flow was thought to be due to both increased blood pressure and vasodilatation (due to increased metabolic activity), because there were not always the parallel changes between blood pressure and cerebral blood flow as described in the results of experiments. Oxygen tension during the convulsion induced by Pentazol in vivo was first measured by Davis et al.\textsuperscript{31} and it was reported that convulsion resulted in the decrease in oxygen tension. Oxygen tension was reported later to rise up during the convulsion by Mochizuki and Kiriike.\textsuperscript{80} In our experiments, PO$_2$ showed definite increase due to increase in blood supply, however, in a few cases the initial slight decrease followed by definite increase was observed, suggesting that the increase in oxygen consumption would take place. PCO$_2$ increased and pH decreased in our experiments indicating the metabolic activation. There are no more problems about the excitatory action of Megimide on the cerebral electrical activity, and mechanism of its action has been discussed. Here in our experiments, the change of Na$^+$ showed a certain correlation with the EEG. It had previously shown that Na ion movement was thought to be influenced by 1) the electrical activity on the brain, 2) the cerebral metabolic activity, 3) pH of the cerebrospinal fluid, and 4) sodium ion concentration of the arterial blood.\textsuperscript{32,33,34} Correlation between Na$^+$ and EEG was in general demonstrated in Fig. 3. When the electrical activity of the brain (EEG) was increased by convulsant drugs the permeability of the cell membrane to

**EXTRACELLULAR Na ION ACTIVITY OF BRAIN**

- **NET Na$^+$ FLUX**
- **EXCITATION**
  - EEG ACTIVATION
  - (AROUSAL, SEIZURE MEGIMIDE)
  - DOMINANT
  - (EARLY RECOVERY FROM ANOxia, ISCHEMIA, ACIDOSIS)
- **AT REST and RECOVERY PATTERNS**
  - EEG RECOVERY
  - (LATER RECOVERY FROM ANOxia, ISCHEMIA, ACIDOSIS)
- **INHIBITION**
  - PRIMARY METABOLIC INHIBITION
  - (ANoXIA, ISCHEMIA, HYPOGlyCemia, BARBITURATES, ACIDOSIS etc.)
- **RESTING**
  - NO INFLUX, EFFLUX
- **EQUAl METABOLIC-EEG ACTIVATION**
- **METABOLIC EXCITATION**
  - (INITIAL EFFECTS of CO2 STIMULATION, GLUTAMIC ACID)
  - DOMINANT METABOLIC RECOVERY
  - (LATER RECOVERY FROM ANOxia, ISCHEMIA, ACIDOSIS)
  - EEG INHIBITION
  - (INITIAL EEG SUPPRESSION BY ANOxia, ACIDOSIS etc.)

Na$^+$ influx correlates with electrical activity (EEG)
Na$^+$ Efflux correlates with metabolic activity (Na PUMP)

Fig. 3. Relationship between the extracellular Na ion activity and metabolic and electrical activity of the brain.

*Japanese Circulation Journal* Vol. 29 May 1965
Na⁺ increased and extracellular sodium ions greatly decreased since many sodium ions appeared to move into the cells as judged by net extracellular measurement. The Na⁺ extruding mechanism which appears to be dependent upon cerebral metabolic activity was then activated to restore the ionic homeostasis. In the EEG activation, therefore, the net initial flux of Na⁺ ion was into cells, hence extracellular Na⁺ ions activity decreased.

**Summary**

The state of convulsion induced by Megimide was investigated by means of concurrent and continuous recording of cerebral blood flow, PO₂, PCO₂, pH, Na⁺, blood pressure and EEG. Cerebral blood flow, PO₂, PCO₂, and blood pressure increased, and pH and Na⁺ decreased. EEG was activated to show the spike activity. Correlation between EEG and the movement of Na⁺ ions was discussed.

**REFERENCES**


