Korean J. of Pharmacology
Vol. 24, No. 2, pp.165-178, 1988

Influence of Electroconvulsive Shock (ECS) on the Central and Peripheral Opiate System of the Rat

Hyuk-Il Kwon*, Kee-Won Kim, Yong-Geun Kwak
Won-Mo Yang and Kyu-Park Cho[1]

Department of Neuropsychiatry, Wonkwang University, School of Medicine, Iri*
Department of Pharmacology, Chonbuk National University Medical School, Chonju, Korea

ABSTRACT

In this study, the effect of single or repeated (daily for 7 or 14 days) electroconvulsive shock (ECS) on central and peripheral opiate system and modification of the actions of ECS by several psychoactive drugs were investigated in the rat.

Repeated ECS caused increase of Met-enkephalin content and decrease of Bmax of specific [^{3}H]imorphine binding in the rat brain. These effects were persisted more than 7 days after the last ECS, but single ECS failed to show these effects. However, β-endorphin content was decreased in midbrain preparation and increased in plasma by repeated or single ECS. These phenomenon was seen shortly after the last ECS. After ECS-induced seizure was prevented by phenobarbital, ECS-induced increase in Met-enkephalin content was significantly attenuated. Imipramine or pargyline did not affect the action of repeated ECS. On the other hand, reserpine, chlorpromazine or haloperidol which were classified as neuroleptic antipsychotics, augmented the ECS-induced changes of central and peripheral opiate parameters. Furthermore, in groups received repeated ECS, changes of Bmax of specific [^{3}H]-morphine binding was inversely correlated with changes of Met-enkephalin contents, but not with changes of β-endorphin contents.

From these results, it is inferred that the central or peripheral opioidergic system may be involved in the therapeutic and/or adverse effects of ECS which also can be influenced by some psychoactive drugs.

Key Words: Electroconvulsive shock, β-endorphin, Met-enkephalin, Antipsychotics, Opiate receptor

INTRODUCTION

The recent discovery of opiate receptor (Pert and Snyder, 1973) and a series of endogenous polypeptide ligands that exhibited specific binding to these receptors (Hughes, 1975) has been followed by massive efforts aimed at defining the role of these substances in both normal and abnormal physiology. Most of these opiate receptors are distributed in corresponding area that major sites of action of opiates in the processing of painful stimuli, *i. e.*; the substantia gelatinosa, the periventricular gray matter, and the medial thalamus. On the other hand, opiate receptors are found at sites that are not primarily concerned with pain sensation.

It has been proposed that these receptors are play certain roles in control of other physiological functions (Pert *et al.*, 1976). By the way, Segal *et al.* (1977) reported that centrally administered β-endorphin induces rigidity and immobility in rats, and Bloom *et al.* (1976) noted that i. v. t. β-endorphin induces a catatonic-like state, reminiscent of some aspects of schizophrenia, reversible with the relatively pure narcotic antagonist naloxone. In addition, it has been observed that the

[1]To whom all correspondences should be addressed.

plasma β-endorphin concentration was increased in the patients of schizophrenia (Brambilla *et al.*, 1984) or endogenous depression (Cohen *et al.*, 1984). These observations strongly suggested that the endogenous opioids play important roles in mental disorders.

The eletroconvulsive therapy (ECT) has long been employed in the treatment of depression and schizophrenia, but the precise mechanism of action is still not clear. There are many reports that suggested the involvement of various neurons. Lerer (1984) reported that long-term electroconvulsive shock (ECS) altered the neuronal activity of monoaminergic and cholinergic nerves in central nervous system. And also, Sackeim *et al.* (1983) reported that therapeutic action of ECT is due to enhanced r-aminobutyric acid (GABA) transmission. Recently, there are many evidences that endogenous opioids are involved in the action of ECT. Thus, there are similarities between the phenomena that produced by opioids and ECS; *i. e.* analgesia (Galligan *et al.*, 1983), catalepsy (Urca *et al.*, 1981, Frenk and Stein, 1984). Izquierdo (1983) observed at ECS induces the release of β-endorphin from pituitary and hypothalamus. Moreover, Yoshikawa *et al.* (1985) reported the increase of preproenkephalin mRNA induced by ECS in hypothalamus and pituitary gland.

In this study, we have attempted to investigate the influence of ECS and/or some antidepressants or antipsychotics on the concentration of endorphins in plasma or midbrain of the rat, and on the specific binding of morphine in the rat brain.

MATERIALS AND METHODS

Animals

Male Sprague-Dawley rats weighing about 200 g were use. The animals were housed in plastic cages with water and food ad libitum.

Electroconvulsive shock (ECS)

The effects of ECS were studied in groups of 6 rats after single ECS and daily ECS for 7 or 14 days of ECS. ECS was delivered transauricularly, through wound clips attached to the pinna of each ear, by alternating current using a stimulator. The stimulus parameters were 1 sec, 60 HZ and 1A. Sham ECS rats subjected to the same procedure without the passage of electrical current. All the procedures were performed between 10 and 11 a. m..

Drug administration

Imipramine, pargyline, reserpine, chlorpromazine or haloperidol was administered twice a day, intraperitoneally. And, phenobarbital was administered 30 min prior to every ECS, i. p..

Assay of Met-enkephalin

The content of Met-enkephalin in the rat brain was quantitated by radioimmunoassay. After decapitation, midbrain was dissected on the ice cold plate. The preparation was homogenized (Polytron, setting 7, 10 sec) in acetic acid (9 ml/g), and neutralized by 1 N NaOH. This homogenate was employed in the RIA of Met-enkephalin. Antiserum and homogenate (or nonlabeled Met-enkephalin in standardization) were mixed with 0.5 ml of 0.2 M Tris buffer (pH 7.4, containing 0.1% albumin and 0.6% dextran) followed by incubation at 4℃ for 18 hrs. Then, 0.2 ml of 1.5% charcoal was added for separation of antibody-bound [^{3}H] Met-enkephalin from free Met-enkephalin. The obtained supernate was counted by liquid scintillation counter (Packard TriCarb).

Assay of β-endorphin

B-endorphin immunoreactivity was quantitated by RIA. Brain tissue was homogenized in 1 N acetic acid (9 ml/g). The homogenate was centrifuged at 10,000× g for 30 mins. The supernate was resuspended with equal vol. of 1 N acetone. The final suspension was evaporated at 20℃ and submitted to RIA by using NEN kit (NEK-003). Extraction of plasma B-endorphin was assayed by the method of Szczudlik and Lypka (1983). Thus, the plasma was mixed with silicic acid (ml/100 mg), and centrifuged at 1,000× g for 2 min. The precipitate was resuspended with 1 ml of distilled water and 1 N HCl, and resuspended with silicic acid. The supernate was washed with acetone and evaporated at 60℃ with air.

Assay of specific morphine binding

The maximum binding (Bmax) and affinity constant (Kd) of the opiate receptor were deter-

mined by the method of Goldstein *et al.* (1976). After decapitation, the brain was removed rapidly and a half of the midbrain was homogenized using a motor driven Tefron-pestle homogenizer in 19 vols of ice-cold 50 mM Tris-HCl buffer (pH 7.4). Tissue preparations were incubated with or without varying concentrations of morphine for 5 mins. Subsequently, [^{3}H]imorphine (specific activity 60 Ci/mM) was added to the reaction mixture and incubated for an additional 15 min period at 37℃. Bound drug was collected on membrane filter (pore size; 0.8 um, nitrocellulose, Whatman) and washed immediately with 15 ml of ice-cold Tris-HCl buffer. The filters were dissolved in 1.0 ml of ethyleneglycolmonomethyleither and assayed for radioactivity by using liquid scintillation counter. Bmax and Kd values are calculated as described by Akera and Cheng (1980).

Protein was assayed by the method of Lowry *et al.* (1951).

Data were analyzed by paired or unpaired student's t-test.

Drugs used were Met-enkephalin (Peninsula), Met-enkephalin antiserum (Peninsula), morphine HCl (Samsung Pharm.), imipramine HCl (Sigma), pargyline HCl (Sigma), reserpine (Sigma), haloperidol HCl (Sigma) and phenobarbital (Sunchundang Pharm.).

RESULTS

Influence of ECS on the opiate system in the rat

Rats were treated with ECS for 1, 7 or 14 days. And, each groups are subdivided into 5 groups according to the duration of treatment in order to examine the acute and chronic effect of ECS.

1. Met-enkephalin content in the rat midbrain

In the control group, the content of Met-enkephalin was 4.7±0.5 ng/mg protein, not different with naive group (4.5±0.6 ng/mg protein). Single ECS did not change this parameter (4.8±0.6 ng/mg protein). In the group treated with ECS for 7 or 14 days, the content of Met-enkephalin was significantly increased from 1 h (7.5±0.8, 9.2±1.0 ng/mg protein) after the last ECS to 7 days (6.5±0.7, 7.6±0.8 ng/mg protein). But at the 14th days after ECS, the content of Met-enkephalin was normalized (5.2±0.6, 5.1±0.6 ng/mg protein) (Fig. 1).

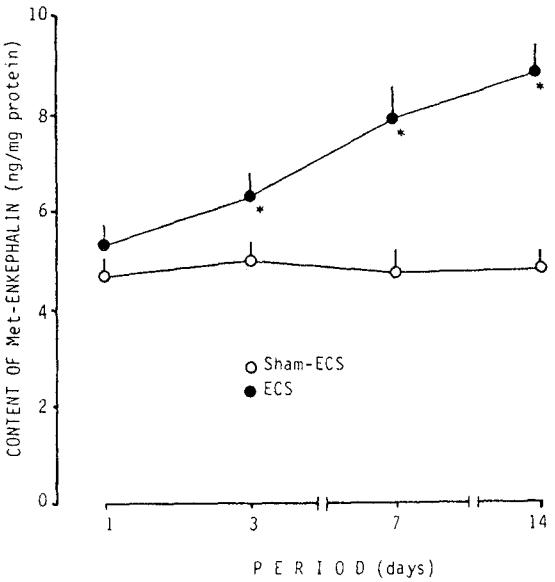

Fig. 1. Changes of Met-enkephalin content of rat midbrain by electroconvulsive shock (ECS). Each point and vertical bar denote the mean and SEM from 6 experiments.
*: Significantly different from the sham-ECS group ($p<0.05$).

2. β-endorphin content in the rat midbrain

The content of β-endorphin in the control groups was 36.5±4.0 ng/g tissue. By the single ECS, the β-endorphin content was decreased (21.8±3.3 ng/g tissue) at 1 h after ECS, but there are no difference from control value at other time points. In the groups treated with ECS for 7 or 14 days, the content of β-endorphin was significantly decreased at 1 h (20.5±3.3, 22.6±2.8 ng/g tissue) after the last ECS and normalized after 24 h of treatment (37.3±4.5, 35.3±4.3 ng/g tissue), as summarized in Fig. 2.

3. Plasma β-endorphin concentration

The concentration of β-endorphin in plasma was 1.62±0.23 ng/ml in the sham-ECS group. In the single ECS-treated group, the plasma β-endorphin concentration was significantly elevated (3.45±0.37 ng/ml plasma) at 5 min after ECS, but rapidly decreased to normal level. And also, in the chronically ECS-treated groups, change of β-endorphin concentration was similar with the single ECS-treated group at correspond-

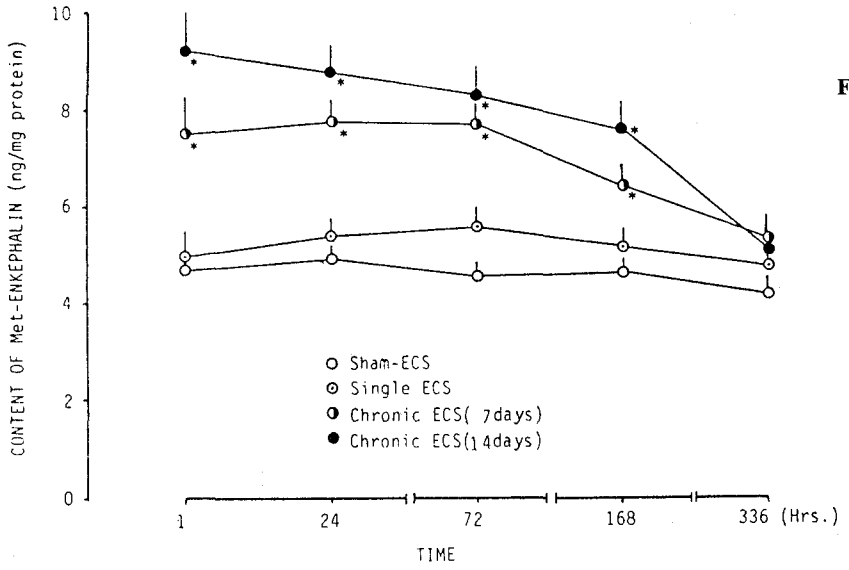

Fig. 2. Influence of electroconvulsive shock(ECS) on Met-enkephalin content in midbrain. Content of Met-enkephalin were measured at various time point after the last ECS. Each point and vertical bar denote the mean and SEM of 6 experiments. *: Significantly different from the sham-ECS group ($p<0.05$).

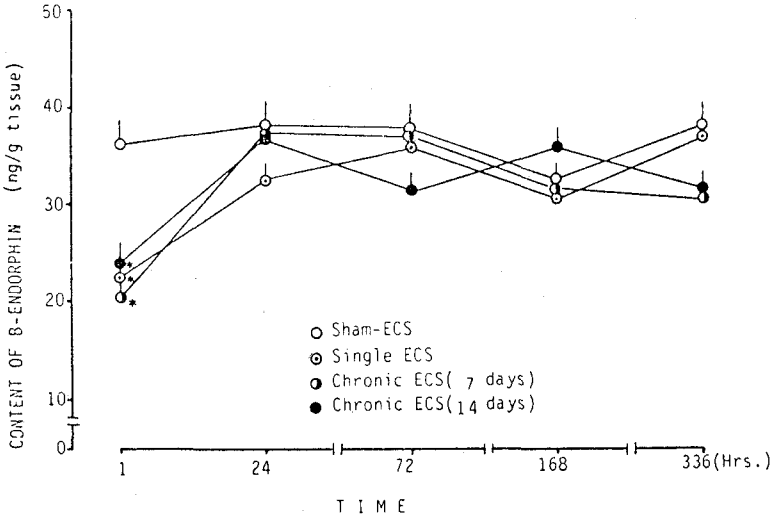

Fig. 3. Influence of electroconvulsive shock(ECS) on β-endorphin content in rat midbrain. Content of β-endorphin was measured at various time point after the last ECS. Other legends are the same as in Fig. 2.

ing time points (Fig. 3).

4. Specific [^{3}H]imorphine binding in the rat midbrain

In the control group, the Bmax of specific [^{3}H]imorphine binding was 0.63 ± 0.05 pmol/mg protein after sham-ECS. By the single ECS, the Bmax was not changed. But, in the groups chronically treated with ECS for 7 or 14 days, the Bmax was significantly decreased at 1 h (0.43 ± 0.04, 0.45 ± 0.05 pmol/mg protein) after the last ECS, and persisted untill 7 days (0.52 ± 0.05, 0.46 ± 0.05 pmol/mg protein). The Bmax of specific morphine binding was recovered to control level at 14th days after the last ECS (Fig. 4). However, the Kd value was not changed in all experimental groups (0.85 ~0.92 nM).

Influence of phenobarbital upon the effects of ECS on the opiate system in the rat

Rats were treated with phenobarbital (100 mg/

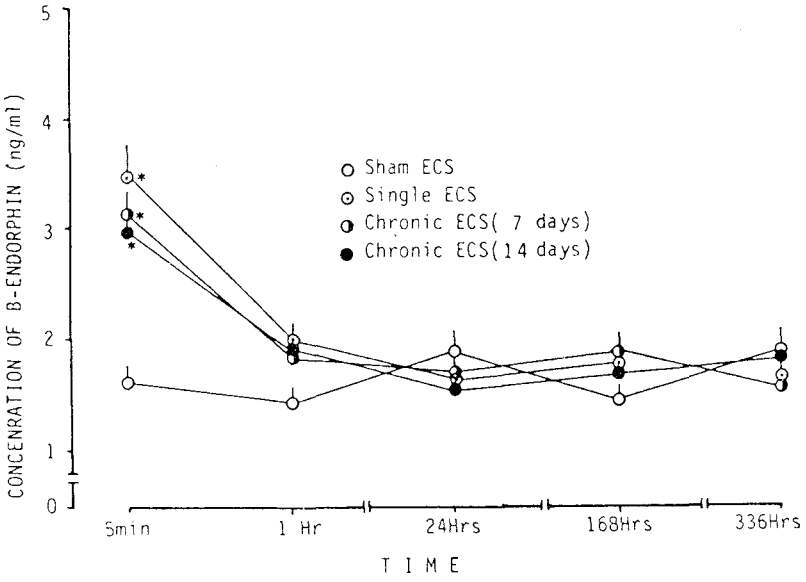

Fig. 4. Influence of electro-convulsive shock(ECS) on concentration of β-endorphin in plasma of the rat. Other legends are the same as in Fig. 2.

Table 1. Influence of phenobarbital (100 mg/kg) on chronic (14 days) ECS-induced changes of opioids peptides contents and specific [^{3}H]-morphine binding in rat brain and plasma

Groups	Met-ENK	β-END	pl. β-END	Bmax
Sham-ECS	17.9±2.5	37.8±4.5	1.62±0.23	0.65±0.06
Chronic ECS (14 days)	33.6±4.1a	22.6±2.3a	2.97±0.32a	0.47±0.05
Phenobarbital	19.5±2.8	48.5±5.1a	3.78±0.29a	0.44±0.04a
ECS with Phenobarbital	21.7±2.6a,b	35.7±3.6b	4.51±0.42a,b	0.32±0.04a,b

Abbreviations and units; Met-ENK: Met-enkephalin (ng/mg protein), β-END: β-endorphin in brain (ng/g tissue), pl. β-END: plasma β-endorphin (ng/ml), Bmax: maximum binding of [^{3}H]-morphine binding (pmol/mg protein). Animals received ECS once a day for 14 days and phenobarbital was injected intraperitoneally 30 min before every ECS. Met-enkephalin content and Bmax of opiate receptor binding were measured at 24 hrs after the last ECS. β-Endorphin content was measured at 1 hr after and 5 min after the last ECS in midbrain preparation and in plasma, respectively.

a: Significantly different from the sham-ECS group ($p<0.05$).

b: Significantly different from chronically ECS group ($p<0.05$).

kg) 30 min before every ECS for 14 days in order to examine the relationship between the effects of ECS and the presence of convulsion. By this dose of phenobarbital itself, the content of Met-enkephalin was not changed, but, the β-endorphin content was significantly increased in the rat brain and plasma, while the Bmax of specific [^{3}H] morphine binding was significantly decreased. However the Kd value was not changed. Pretreatment with phenobarbital inhibited the convulsion induced by ECS. In this case, the increase of Met-enkephalin content in the rat brain induced by ECS was significantly attenuated. But the effects of chronic (14 days) ECS (the decrease of Bmax of specific [^{3}H] morphine binding and β-endorphin content in midbrain, increase of the concentration of β-endorphin in plasma) were not influenced (Table 1).

Influence of various psychoactive drugs on the effects of ECS on the opiate system of the rats

In this experiment, we exammed the influences of antidepressants, imipramine and pargyline, or

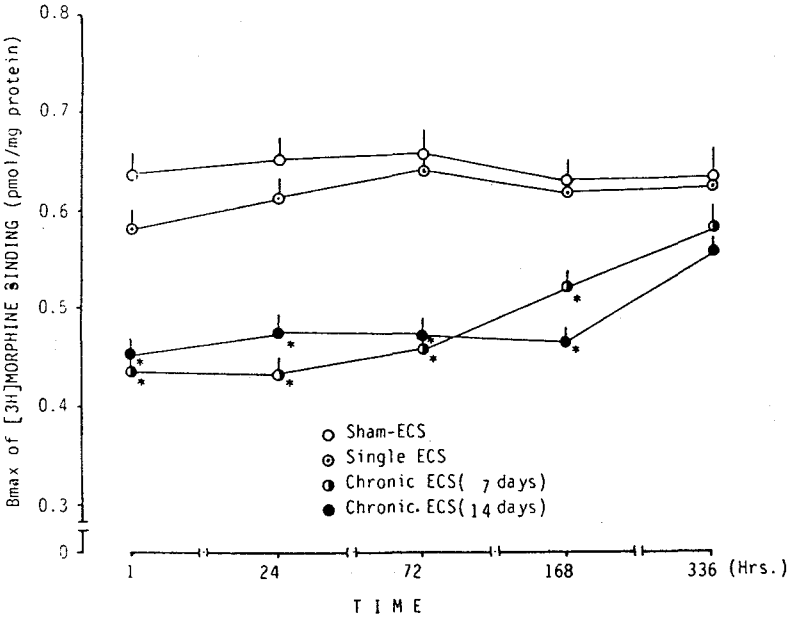

Fig. 5. Influence of electroconvulsive shock on specific [^{3}H]-morphine binding in rat midbrain.
Kd values did not changed in all experimental groups. Other legends are the same as in Fig. 2.

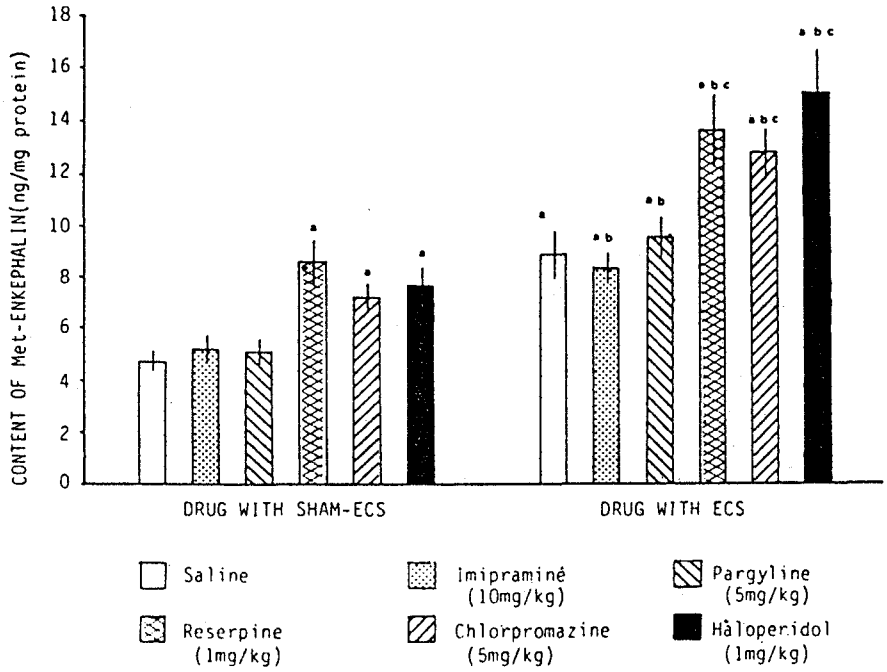

Fig. 6. Influences of chronic treatment of imipramine, pargyline, reserpine, chlorpromazine and haloperidol on the ECS-induced change of Met-enkephalin content in rat midbrain. Animals received ECS once a day, and each drugs was administered intraperitoneally twice a day for 14 days. Met-enkephalin contents were measured 24 hrs after the last ECS. Each value and vertical bar denote the mean with SEM from 6 experiments.
a: Significantly different from the saline with sham-ECS group ($p<0.05$). b: Significantly different from the corresponding drug-treated group ($p<0.05$). c: Significantly different from saline with ECS group ($p<0.05$).

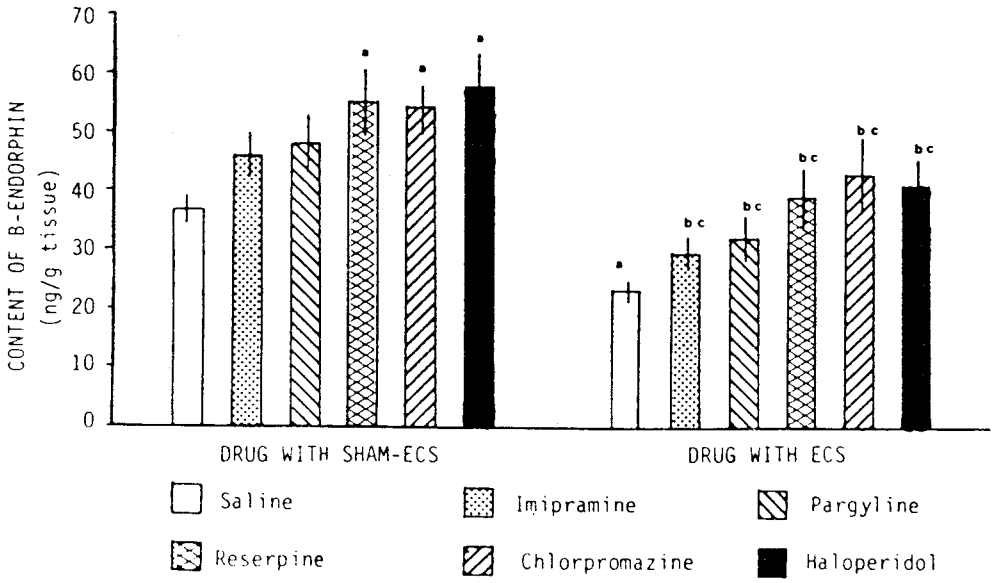

Fig. 7. Inflaence of various psychoactive drugs on the ECS-induced decrease of β-endorphin content in rat midbrain
β-endorphin contents were measured at 1 hr after the last ECS.
Others are the same as in Fig. 6.

antipsychotics, reserpine, chlorpromazine and haloperidol, on the actions of ECS on the opiate system in the rats. Each drugs administered twice a day for 14 days with or without ECS, intraperitoneally.

1. Met-enkephalin content in the rat brain

Imipramine (10 mg/kg/day) or pargyline (5 mg/kg/day) affect neither the Met-enkephalin content of the rat brain nor the effect of ECS, while, reserpine (1 mg/kg/day), chlorpromazine (5 mg/kg/day) or haloperidol (1 mg/kg/day) increased the content of Met-enkephalin in the rat brain. And also, the amplitude of increase was more prominent in the group treated with ECS and simultaneously with each drug than in the group treated with the drug or treated with ECS (Fig. 5).

2. β-endorphin content in the rat brain

After 14 days of ECS, β-endorphin content in the rat brain was 22.6 ± 2.8 ng/g tissue, which was significantly decreased compared with the control value. Chronic administration of imipramine or pargyline increased the β-endorphin content in the rat brain. In the group treated with ECS and simultaneously with drugs, the β-endorphin content was lower than that of drug treated group, but greater than in the ECS-treated group. On the other hand, β-endorphin content in the rat brain was significantly increased by the treatment with reserpine, chlorpromazine or haloperidol. In these group, ECS increased β-endorphin content in plasma (Fig. 6).

3. Plasma β-endorphin concentration

The plasma β-endorphin concentration was 1.56 ± 0.21 ng/ml in the control group. In the group of chronically ECS-treated group, plasma β-endorphin was significantly increased. Chronic treatment with imipramine or pargyline increased the plasma β-endorphin concentration. The plasma β-endorphin concentration in the drug-and ECS-treated group was greater than that in drug-or ECS-treated group. After the 14 days of treatment with reserpine, chlorpromazine or haloperidol, the plasma β-endorphin concentration was significantly increased. In these group, ECS increased the plasma β-endorphin concentration (Fig. 7).

4. Specific [^{3}H] morphine binding in the rat brain

In the control group, the Bmax of specific [^{3}H] morphine binding was 0.64 ± 0.05 pmol/mg pro-

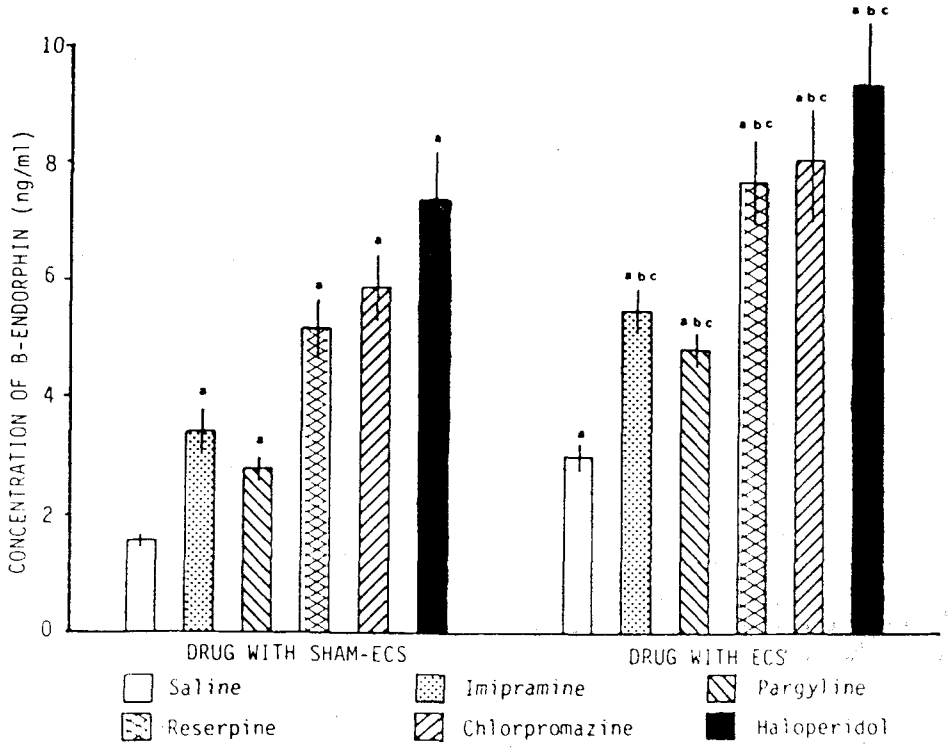

Fig. 8. Influence of various psychoactive drugs on the ECS-induced change of plasma β-endorphin concentration in rat. Plasma β-endorphin concentration was measured at 5 min after the last ECS. Others are the same as in Fig. 6.

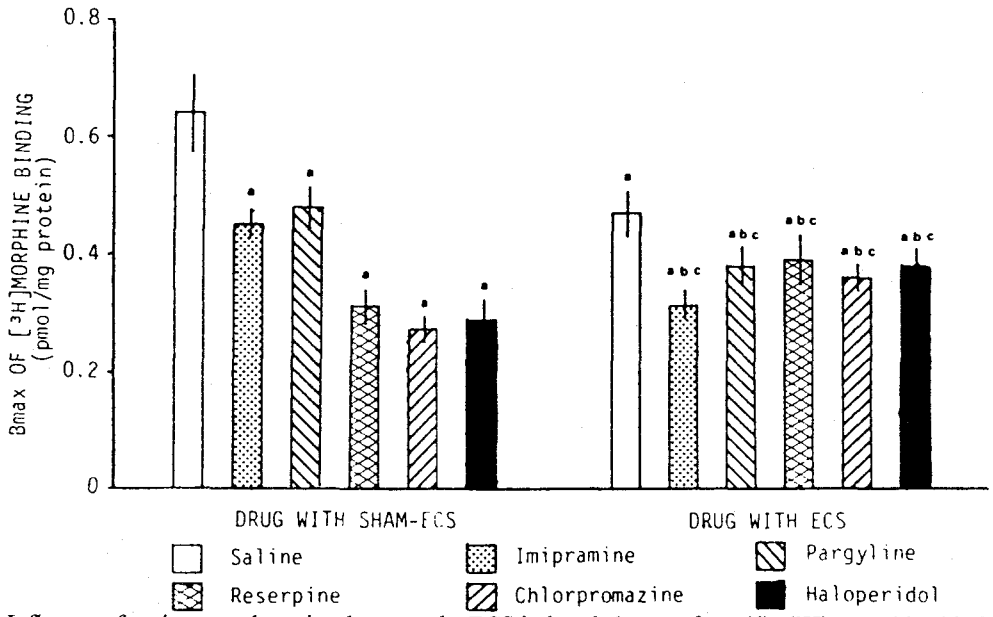

Fig. 9. Influence of various psychoactive drugs on the ECS-induced change of specific [^{3}H]-morphine binding in rat midbrain.

Specific opiate binding was measured at 24 hrs after the last ECS. Others are the same as in Fig. 6.

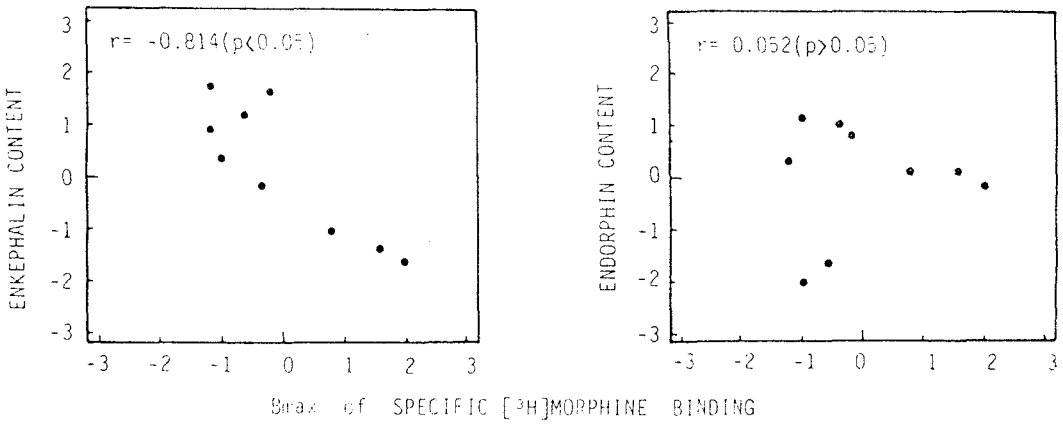

Fig. 10. Correlation between Bmax of [^{3}H]-morphine binding and Met-enkephalin content (left panel) or β-endorphin content (right panel) in midbrain of the rat received ECS once a day for 7 or 14 days.

tein, and this value was significantly decreased in the group of chronically ECS-treated group (0.47±0.05 pmol/mg protein). Chronic treatment of imipramine, pargyline, reserpine, chlorpromazine or haloperidol decreased the Bmax of [^{3}H] morphine binding. In these groups, ECS increased the Bmax of the ligand (Fig. 8), while, the Kd value was not changed in these all experimental groups.

Correlation between the specific [^{3}H]morphine binding and opioid peptides in the rat brain

In the groups of ECS-treated for 7 or 14 days, the content of Met-enkephalin was well correlated with the Bmax of specific [^{3}H] morphine binding, negatively ($r=-0.814$, $p<0.05$), but the Bmax of specific [^{3}H] morphine binding did not show any correlation with the content of β-endorphin in the rat brain (Fig. 9).

DISCUSSION

In this experiment, the Met-enkephalin content in rat brain was increased from the 1 h after the last ECS and persisted for 7 days in the repeated (daily for 7 or 14 days) ECS groups, except in the single ECS-treated group.

Although the mechanism of therapeutic action of ECT (electroconvulsive therapy) in treatment of depression and schizophrenia was poorly understood, there are many suggestions that endogenous opioids are involved. Recently, release of endorphins from hypothalamus and pituitary gland by ECS (Izquierdo, 1983) has been observed and Yoshikawa *et al.* (1985) also reported the increase of preproenkephalin mRAN in hypothalamus by repeated ECS. Our result provides another evidence to the involvement of endogenous opioids in the action of ECT. Clinically, the symptoms of depression and schizophrenia were improved by repeated ECS and persisted for some periods after ECSs, but not by single ECS (Kety, 1974) was consistent with our result.

β-Endorphin was mainly derived from the proopiomelanocortin (POMC) in pituitary gland and hypothalamus, released in CSF or blood, and produces various effects, such as analgesia (Tari *et al.*, 1983, Hart *et al.*, 1983), catalepsy (Katz, 1980), changes in locomotion (Katz, 1980), in body temperature (Blasig *et al.*, 1978), in memory (Izquierdo, 1983) and in release of certain hormones (Moretti *et al.*, 1983) and in release of certain hormones (Moretti *et al.*, 1983). Many investigators are observed the similar phenomena after ECS in animals (Galligan *et al.*, 1983, Urca *et al.*, 1981, Frenk and Stein, 1984, Meco *et al.*, 1978). In this experiment, the rat brain β-endorphin content was decreased 1 h after the last ECS in single or repeated ECS-treated group. This phenomenon can be regarded as a result of the release of β-endorphin into CSF thereby decrease in brain tissue. Meco *et al.* (1978) and Lewis *et al.* (1981) reported that the analgesia and changes in blood pressure and heart rate were persisted for about 1 h after the ECS.

These results are consistent with our result in functional aspects. And also, in this experiment,

blood concentration of β-endorphin was increased 5 min after the last ECS and normalized at 1 h after ECS in single or repeated ECS-treated groups. Emrich *et al.* (1979), Alexopoulos *et al.* (1983) and Misiazek *et al.* (1984) were reported similar results. Rossier *et al.* (1979) suggested the independent β-endorphin pools in the CNS and periphery. And Guillemin *et al.* (1977) observed the concomittant increase of β-endorphin and ACTH in the pituitary gland. With this results, it is suggested that the ECS could affect the endorphin regulation in pituitary and hypothalamus. But, in the view of the alterlation of permeability of the blood-brain barrier (Awasthi *et al.*, 1982), we could not exclude the possibility that the leakage of this peptide from brain. The relatively short duration of increase of β-endorphin in blood was due to the rapid destruction in blood (Graf *et al.*, 1979).

In this study, the β-endorphin contents in brain and blood also by single as well as repeated ECS, were also changed only in shortly after the ECS unlike that of Met-enkephalin. These results are inferred that β-endorphin may involve only in the acute action of ECS, such as analgesia (Lewis *et al.*, 1981) and loss of memory (Izquierdo, 1983), but not in the long-lasting therapeutic action of ECT in depression and schizophrenia.

Since it has been shown that the ECT not accompanying with convulsion could not improve the symptoms of depression (Fink, 1974), we examined the influence of phenobarbital on the effects of ECS in the rats. In this experiment, phenobarbital, an anticonvulsant, attenuated the ECS-induced increase of Met-enkephalin content in the rat brain. Cronholm and Ottossen (1960) reported that therapeutic effect of ECT was inhibited by shortening of duration of convulsion using local anesthetics. And, brain content of Met-enkephalin increased also in the rat which have shown seizures induced by kainic acid (Hong *et al.*, 1980).

Regarding these and our results, it is suggested that induction of seizures is the essential part of therapeutic effects of ECT, and that this seizures are closely related to Met-enkephalin content in the brain. Sackeim *et al.* (1983) suggested that anticonvulsant and antidepressant effects of ECT are due to enhanced GABA transmission and that localized suppression of neural metabolic activity is associated with therapeutic response to ECT. Then, phenobarbital caused the increase of β-endorphin content in the rat brain and plasma and the decreased of Bmax of specific morphine binding in the rat brain. Our previous paper reported the similar results in the pineal gland and in midbrain of the rat (Park *et al.*, 1985, So *et al.*, 1986). It has been shown that the anesthetic action (Gilbert and Martin, 1977, Horita and Carino, 1978) and antiovulatory action (Marton *et al.*, 1980) of pentobarbital were inhibited by naloxone, a narcotic antagonist. These results suggests the involvement of endogenous opioids in the action of barbiturates.

On the contrary, phenobarbital could not affect the decrease of Bmax of specific morphine binding and β-endorphin content in rat brain, and the increase of β-endorphin content in plasma induced by ECS. We interpret this result as ECS-induced seizures are not related with β-endorphin but to Met-enkephalin.

In our study, imipramine and pargyline caused the increase of β-endorphin content in the brain and plasma, and the decrease of Bmax of specific morphine binding in the rat brain, but, did not alter the content of Met-enkephalin in the rat brain. And the effects of ECS were also affected by any of these drugs. It is widely accepted that these clinically used antidepressants were exert their effect by normalizing or balancing the imbalance of neurotransmission of biogenic amines in the central nervous system. This hypothesis was supported by the fact that the sensitivity of alpha 2 -adrenoceptor, serotonergic receptor and dopaminergic receptor are changed by chronic treatment with antidepressants (Banerjee *et al.*, 1977, Vetulani *et al.*, 1980, Metz and Heal, 1986, and Chiodo and Antelman, 1980).

Recently, there are increasing evidences that the involvement of endogenous opioids in the therapeutic action of antidepressants. De Felipe *et al.* (1986) reported the naloxone-reversible analgesic action of antidepressants. Isenberg and Cicero (1984) observed the potentiation of analgesic effect of morphine by antidepressants. Furthermore, it has been reported that the displacement of naloxone or Met-enkephalin from the opiate receptor by antidepressants (Liu and Wang, 1981). In our previous paper (Jung *et al.*, 1984), antidepressants are capable of alteration of the receptor binding characteristic of [^{3}H]imorphine as well as the content of β-endorphin concentration was increased by imipramine or pargyline in this experiment. Knepel *et al.* (1981) reported that the catecholamines, esp. β-agonist, could elicit the release of β-endorphin from pituitary gland. From this

view, increase of β-endorphin concentration in this experiment might be due to the increase of bioavailability of circulating catecholamines by imipramine or pargyline. Angst *et al.* (1979) observed the beneficial effect of IV β-endorphin in the patients of depression. Here, we thought that the alteration of plasma β-endorphin concentration could be a factor of antidepressant action of these drugs. But, in this experiment, the effects of those antidepressants were differ from the ECS in many aspects, and they could not influence on the effects of ECS. Accordingly, it has suggested that the mechanism of action of these antidepressants and ECS were different from each other.

In other experiment, long-term treatment with antipsychotics, reserpine, chlorpromazine or haloperidol increased the Met-enkephalin in the brain, and β-endorphin in the brain and plasma. These drugs are clinically used as antipsychotics. It has been proposed that the mechanism of action of drugs was mainly due to the stimulation of turnover rate of dopamine in central nervous system. Then, it was observed that the opiates or opioids increase the turnover rate of dopamine in corpus striatum, (Carenzi *et al.*, 1975, Perez *et al.*, 1979). Moreover, this action of opiates was antagonized by naloxone (Costa *et al.*, 1973). And, Locatelli *et al.* (1983) observed the decrease of opioids content by dopaminergic agonists. This results suggest that there are close relationship between opioidergic and dopaminergic neurons in central nervous system.

Recently, Weis and Stein (1979), Hollt *et al.* (1979) and Hong *et al.* (1979) reported the increase of opioids by chronically treated animals with antipsychotics. And, Kline *et al.* (1977) observed the improvement of symptoms by administration of β-endorphin in patients with schizophrenia and depression. These results suggested that endogenous opioids are plays a important role in the therapeutic action of antipsychotics. In this experiment, there are more prominent increase in the content of Met-enkephalin in brain as well as plasma β-endorphin concentration than in the rat with drug-or ECS-only treated one. It has been observed that ECT increased haloperidol neuroleptic activities in plasma and red blood cell (Aoba *et al.*, 1983). Furthermore, Salzman (1980) reported greater short term improvement scores for patients treated with ECT and chlorpromazine than for those treated with ECT alone. This result could be a clue to the assessment of efficacy of ECT and/or drug therapy in treatment of mental illness. However, the efficacies of theses therapies are still subject of debate.

The Bmax of specific [^{3}H] morphine binding was negative correlated with the content of Met-enkephalin in the brain, but not with β-endorphin. This phenomenon can be interpreted as a result of receptor regulation.

In summary, though our results are not enough to describe the antidepressant and antipsychotic actions of ECT, it is suggested that the endogenous opioids are involved, as least in a part, in therapeutic mechanism of ECT and antipsychotic drugs can modulate central opiate system.

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=국문초록=

백서의 중추와 말초 Opiate계에 미치는 전기충격의 영향

원광대학교 의과대학 신경정신과학교실* 및 전북대학교 의과대학 약리학교실

권혁일* · 김기원 · 곽용근 · 양원모 · 조규박

백서에서 전기충격(electroconvulsive shock; ECS)이 뇌내 및 혈중 opiate system에 미치는 효과와 이에 대한 수종의 psychoactive drugs의 영향을 검토코저 1일 1회씩, 1, 3, 7 및 14일간 ECS를 가하거나, 14일간 상기 약물과 ECS를 병행처리한 백서의 뇌내 specific [^{3}H]-morphine binding, Met-enkephalin 함량, β-endorphin 함량 또는 혈중 β-endorphin 농도를 측정하여 다음과 같은 결과를 얻었다.

1. 뇌내 Met-enkephalin의 함량은 1회의 ECS에 의해서 증가되는 경향을 보였으며 장기간의 ECS를 가한 군에서는 최종 ECS 1시간 후부터 유의하게 증가되어 7일후까지 지속되었다.

2. 뇌내 β-endorphin의 함량은 ECS처리 횟수에 관계없이 최종 ECS 1시간후에는 유의하게 감소되었으나 24시간, 3일, 7일 및 14일후의 측정치는 대조군과 차이가 없었다.

3. 혈중 β-endorphin의 농도는 ECS처리 횟수에 관계없이 최종 ECS 5분후에 유의하게 증가되었으나 1시간, 24시간, 7일 및 14일후의 측정치는 대조군과 차이가 없었다.

4. 뇌내 specific [^{3}H]-morphine binding의 Bmax는 1회의 ECS에 의해 변동되지 않았으나 장기간의 ECS를 가한 군에서는 ECS 1시간후부터 유의하게 감소되어 7일후까지 지속되었다. 한편 Kd치는 모든 실험군에서 변동되지 않았다.

5. ECS 장기처리군에서 ECS 30분전 phenobarbital(100 mg/kg) 전처리는 ECS에 의한 뇌내 Met-enkephalin 함량증가를 현저히 억제 하였으며, ECS에 의한 뇌내 specific [^{3}H]-morphine binding의 Bmax 감소, 뇌내 β-endorphin 함량감소와 혈중 β-endorphin 농도증가에 대해서는 영향을 주지 못하였다.

6. Imipramine 또는 pargyline 장기처리는 자체로써 뇌내 β-endorphin 함량증가, 혈중 β-endorphin 농도증가, 뇌내 specific [^{3}H]-morphine binding의 Bmax 감소를 일으켰으나 뇌내 Met-enkephalin의 함량과 ECS 작용에 영향을 미치지 못했다.

7. Reserpine, chlorpromazine 또는 haloperidol 장기처리는 자체로써 뇌내 Met-enkephalin의 함량증가, 뇌내 β-endorphin 함량증가, 혈중 β-endorphin 농도증가, 뇌내 specific [^{3}H]-morphine binding의 Bmax 감소를 일으켰고, ECS 효과를 강화시켰다.

8. 장기간 ECS를 가한 백서의 뇌내 specific [^{3}H]-morphine binding의 Bmax는 뇌내 Met-enkephalin 함량과는 유의한 역상관 관계를 보이나 뇌내 β-endorphin 함량과는 관계가 없었다.

이상의 실험성적은 전기충격요법이 생체내에서의 작용기전에 중추 또는 말초 opiate계가 개입되어 있음을 시사하며 또한 ECT의 효과가 수종의 중추신경계에 작용하는 약물에 의해 변동될 수 있음을 보여준다.