Electroconvulsive seizure (ECS) therapy is a clinically proven treatment for depression and is often effective even in patients resistant to chemical antidepressants. However, the molecular mechanisms underlying the therapeutic efficacy of ECS are not fully understood. Here, I review studies that show molecular, cellular, and behavioral changes by ECS treatment, and discuss the functions of ECS to underlie the action of antidepressant effects. In hippocampus, these changes cover gene induction, increased adult neurogenesis, and electrophysiological reactivity. Especially, the role of vascular endothelial growth factor (VEGF) in neurogenesis is discussed. Among other gene expression changes in hippocampus, a role of cyclooxygenase (COX)-2, an inducible type of the rate-limiting enzyme of prostanoid synthesis, is focused. ECS-induced changes in other brain regions such as prefrontal cortex and hypothalamus, and ECS-induced behavioral changes are also reviewed. Understanding the molecular, cellular, and behavioral changes by ECS will provide a new view to find potential targets for novel antidepressant design that are highlighted by these findings.

Key words antidepressant; electroconvulsive seizure; hippocampus; gene expression; neurogenesis; cyclooxygenase

1. INTRODUCTION

Mood disorders are among the most common forms of mental illness and are a leading cause of suicide.\(^1\) Although chemical antidepressants such as selective serotonin or noradrenaline reuptake inhibitors (SSRIs, SNRIs, respectively) are widely prescribed, therapeutic responses to these treatments require weeks and are realized in only a subset (approximately 60—70%) of patients.\(^2\) For many patients who do not respond to such drugs, electroconvulsive seizure (ECS) therapy is a highly effective and rapid alternative treatment.\(^3,4\) However, the exact mechanisms underlying the actions of ECS therapy are not yet understood. Thus, identification of the relevant therapeutic actions of ECS treatments could lead to faster-acting and more effective therapies than currently available chemical antidepressants.

In this review, I focus on molecular and cellular changes induced by ECS models in several brain regions, particularly the hippocampus, and consider the involvement of ECS in behavioral actions and its potential for finding new therapeutic targets in depression.

2. ECS-INDUCED GENE REGULATION AND NEUROGENESIS IN HIPPOCAMPUS

Recent Advances The molecular effects of ECS are diverse and include changes in levels of neurotransmitters, gene expression, synaptic remodeling, and cell proliferation (Fig. 1A). During the last 10 years, extensive studies have investigated molecular and cellular changes induced by ECS in the hippocampus including gene regulation and neurogenesis. This section will provide a brief summary of these topics.

Regulation of Gene Expression in Hippocampus by ECS Treatment Recent studies for identification of the relevant actions of antidepressant treatments including ECS have focused on intracellular signal-transduction pathways and analysis of target genes.\(^5-7\) These alterations are thought to mediate long-lasting changes in cell morphology and function to underlie the action of antidepressants in part. ECS treatment is the most robust gene inducer among all antidepressant treatments especially in the hippocampus. Among those genes, induction of neurotrophic/growth factors has been extensively studied. These are the brain-derived neurotrophic factor (BDNF) and other growth factors such as vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF)-2.\(^8-10\)

BDNF, a member of the nerve growth factor family, has been shown to increase synaptic strength, survival, and growth of mature neurons through activation of a transmembrane receptor, TrkB. Expression of BDNF and TrkB is regulated by short- and long-term ECS treatment.\(^8\) A single ECS treatment results in 10—20-fold induction of BDNF gene after ECS in rat hippocampal dentate gyrus. Long-term ECS treatment (once daily for 7—10 d) also induces BDNF mRNA. The extent of induction is decreased relative to the level of that observed after a single induction. However, the level of BDNF mRNA remains increased for a longer time after long-term ECS compared with a single ECS treatment.

VEGF and FGF-2 mRNA in rodent hippocampus is also increased after acute and chronic ECS treatment.\(^9,11\) These factors were originally found mitogenic factors for non-neuronal cells such as endothelial cells and fibroblasts, but now they are also accepted as neurotrophic and neuroprotective factors.\(^12\)

Administration of neurotrophic/growth factors directly into the hippocampus or lateral ventricles has been shown to mimic antidepressant effects in animal models. For instance, infusions of BDNF into the hippocampus decrease immobility time in the forced swim test similar to the behavioral effects of antidepressants.\(^13\) Infusions of VEGF into the lateral ventricles mimic the action of antidepressants in multiple behavioral models.\(^10\) These findings indicate that neurotrophic/growth factors are strong candidates to mediate antidepressant effects by ECS treatment, at least in part.

ECS treatment also increases expression of several neuropeptide molecules such as neuropeptide Y (NPY), thyro-
tropin-releasing hormone (TRH), and VGF. Increase of NPY mRNA in the hippocampus was observed especially after chronic ECS treatment. The antidepressant-like effects of NPY have been studied. In the forced swim test, acute administration of NPY into the lateral ventricles produced an antidepressant effect in naïve rodents. In addition, in the learned helplessness model, acute infusion of NPY in the CA3 of the hippocampus produced an antidepressant-like effect. TRH mRNA increases occurred only after chronic ECS in the hippocampus. This increase is consistent with the ability of ECS to increase prepro-TRH peptides in several rat brain regions and with the antidepressant-like effects of TRH in the rodent forced swim test. VGF is a neuropeptide precursor with a restricted pattern of expression in the central nervous system. VGF was originally identified on the basis of its rapid and robust regulation by nerve growth factor in PC12 cells, and other stimuli such as exercise and neuronal activity also induce VGF mRNA in a subset of neurons. Expression of VGF mRNA is increased by both acute and chronic ECS in the dentate gyrus of the hippocampus. Among them, I will focus on COX-2, a critical enzyme of prostanoid production, in a later section and discuss a role of COX-2 products in the hippocampus (Fig. 1B).

Increased Neurogenesis in Hippocampus by ECS Treatment

It is now clear that neuronal cell birth or neurogenesis occurs in the adult dentate gyrus region of the hippocampus. The antidepressant-like effects of NPY have been studied. In the forced swim test, acute administration of NPY into the lateral ventricles produced an antidepressant effect in naïve rodents. In addition, in the learned helplessness model, acute infusion of NPY in the CA3 of the hippocampus produced an antidepressant-like effect. TRH mRNA increases occurred only after chronic ECS in the hippocampus. This increase is consistent with the ability of ECS to increase prepro-TRH peptides in several rat brain regions and with the antidepressant-like effects of TRH in the rodent forced swim test. Since blockade of cell proliferation by irradiation blocked the actions of antidepressants in the novelty-suppressed feeding and the chronic unpredictable stress paradigms, it is suggested that induction of neurogenesis is re-
quired for antidepressant action, at least in part.

Interestingly, ECS is a more potent stimulator of proliferation than chemical antidepressants. ECS increases cell proliferation by 2.5—4 fold compared with about 1.5 fold for chemical antidepressants. In addition, while the neurogenic action of antidepressants requires chronic treatment (14—21 d), ECS can start neurogenic action within 3 d after a single seizure. Two major subclasses of proliferating cells in the subgranular zone (SGZ) in the dentate gyrus have been characterized: neural stem cells and neural progenitor cells. Segi-Nishida et al. showed that ECS increases proliferation of neural stem cells at an early mitotic phase then increases that of neural progenitor cells at a later phase in SGZ of the hippocampus. On the other hand, it was reported that chronic administration of the SSRI fluoxetine only increases proliferation of neural progenitor cells in the hippocampus without affecting neural stem cell proliferation. This accounts for the superior efficacy of ECS of hippocampal cell proliferation and neurogenesis. Consistently, blockade of VEGF signaling inhibits induction of proliferation by ECS treatment. In contrast, BDNF is required for antidepressant regulation of survival of newborn neurons, although not the proliferation.

As mentioned above, rapid progress has been made in understanding the mechanisms underlying the neurogenic actions of antidepressants including ECS. VEGF signaling is now considered as a main factor to mediate increase of proliferation by ECS as well as other antidepressants (Fig. 2B). First, the time—course for induction of VEGF by ECS in the dentate gyrus of the hippocampus is consistent with that of neurogenesis. Second, VEGF infusion into lateral ventricles is sufficient to increase both neural stem and progenitor cells in SGZ of the dentate gyrus. More importantly, blockade of VEGF signaling inhibits induction of proliferation by ECS treatment. In contrast, BDNF is required for antidepressant regulation of survival of newborn neurons, although not the proliferation. As mentioned above, rapid progress has been made in understanding the mechanisms of gene regulation and neurogenesis by ECS treatment in the hippocampus during the past 10 years. However, there are numerous unanswered questions that need to be addressed about the molecular, cellular, and behavioral effects of ECS. In the next section, I will focus on the effect of ECS on mature neurons of the dentate gyrus in the hippocampus.

3. MORPHOLOGICAL AND FUNCTIONAL CHANGES IN MATURE NEURONS OF DENTATE GYRUS BY ECS TREATMENT

Facilitated neurogenesis by ECS may alter functional roles of the dentate gyrus in the hippocampal circuit. However, since the number of additional new neurons would be only a few percent of the total granule cells, the principal neurons of the dentate gyrus, the modification of functions of existing granule neurons by ECS treatment would also be important for antidepressant actions. Neural stimulation by ECS induces c-fos expression, a marker for neural activation, in granule cells, as well as other gene induction such as BDNF and COX-2 described in the previous section. This suggests that ECS treatment activates mature granule cell neurons. Then, what kind of morphological and functional changes are induced by ECS in mature granule cells? To investigate this, several studies were done in late 1990s.

Chronic ECS treatment induces sprouting of the granule cell mossy fiber pathway, which provides the primary input to CA3 pyramidal cells, in the hippocampus, whereas chronic administration of chemical antidepressants such as fluoxetine were ineffective. This indicates that induction of mossy fiber sprouting by ECS is not a common property of antidepressant therapies. It is possible that the ability to induce sprouting might related to the superior efficacy of ECS therapy when compared with chemical antidepressants clinically. Alternatively, it may contribute to the transient cognitive impairment that accompanies ECS in humans.

Electrophysiological changes in granule cell neurons by ECS treatment were also examined. Chronic ECS treatments enhance baseline levels of synaptic transmission in the dentate gyrus. On the other hand, the level of experimentally induced long-term potentiation (LTP) is reduced by ECS. This reduction of LTP in ECS-treated animals could occur by saturation of the potential to induce additional synaptic plasticity in granule cells. These electrophysiological changes are observed in fluoxetine-treated animals to a similar extent to that in ECS-treated animals. These findings suggest that ECS as well as chemical antidepressants induce LTP-like synaptic changes, which may relate to stress-protective or cognitive improvement mechanisms in granule cells of the dentate gyrus.

Recently, interesting phenotypic changes of granule cell neurons were reported in chemical antidepressant-treated animals. Chronic fluoxetine treatment in mice strongly reduced expression of a mature granule cell marker, calbindin. The fluoxetine-treated granule cells also exhibit immature-like functional characteristics showing increased excitability of granule cells and reduced mossy fiber synaptic facilitation. These results suggest that chronic fluoxetine treatment reverses the phenotypic maturation of adult dentate granule cells especially in the functional aspect of maturation. Since chronic fluoxetine treatments have also been shown to accelerate early maturational processes by inducing neurogenesis, this treatment seems to have bidirectional effects on granular cell maturation, dependent on the maturational stage of the cells. It is interesting whether ECS treatments or stress stimuli also induce phenotypic changes of granular cells, and if so, what signaling mediates to induce the changes. The causal role of “dementated” neurons in the behavioral actions of antidepressants will be also investigated.

4. POSSIBLE ROLES OF ECS-INDUCED COX-2 IN HIPPOCAMPUS

COX enzyme catalyzes the first step in the synthesis of prostanoids including prostaglandins and thromboxane and exists in two isoforms, COX-1 and COX-2. Nonsteroidal anti-inflammatory drugs such as indomethacin and aspirin inhibit COX activity, leading to block prostanoid synthesis. In the central nervous system, COX-2 is expressed constitutively and also increased in neurons of the hippocampus by various stimuli such as seizure and cerebral ischemia.

Both a single and chronic ECS treatments result in 20—40-fold induction of COX-2 gene in the hippocampus especially in granule cells of the dentate gyrus (Fig. 1B).
However, the role of ECS-induced COX-2 remains largely unknown. In this section, I will summarize the role of COX-2 in the hippocampus and discuss possible effects of ECS-induced COX-2 on memory retention, neuroprotection, and neurogenesis.

Clinically, ECS therapy induces retrograde amnesia, which refers to loss of previously acquired memories, and this is an important reason that utilization of ECS therapy is low. Recently, one group suggested involvement of COX-2 in ECS-induced retrograde amnesia. Administration of five ECSs resulted in significant retrograde amnesia on the step-down passive avoidance task in rats. This memory impairment was significantly protected by chronic treatment with celecoxib, a COX-2 inhibitor, suggesting that COX-2-dependent prostanoids are involved in ECS-induced memory impairment. However, in physiological condition, several studies showed that prostanoids are involved in hippocampus-dependent memory formation, and LTP formation at the perforant path-dentate gyrus synapse in the hippocampus. Although the reason for the opposite effects of COX products on memory formation in different situations remains unknown, it should be pointed out that the magnitude of ECS-induced COX-2 upregulation is extremely high by hyperstimulation. It is possible that nonphysiological COX-2 induction leads to neuronal excitotoxic changes contributing to cognitive impairment. Thus it is interesting to examine how ECS-evoked COX products of prostanoids affect electrophysiological properties such as LTP formation in hippocampal neurons so as to analyze the involvement of COX-2 in ECS-induced memory impairment.

Chemically induced seizures such as kainic acid-induced seizure also induce COX-2 gene expression in the hippocampus. It is known that local or systemic administration of kainic acid induces hippocampal neural loss. The effects of COX inhibitors on kainic acid-induced neural cell death have been examined. One study showed that pretreatment with the COX-2 inhibitor NS-398 aggravates kainic-acid-induced neural cell death and extends lesions to CA1 and CA3 regions of the hippocampus, while another study indicated that treatment with another COX-2 inhibitor, rofecoxib, after kainic-acid injection reduces neural cell death in the CA1 and CA3 regions. These studies suggest that the time-course and species of prostanoid production are important to determine the neuroprotective or neurotoxic effects of prostanoids. Since it has been reported that ECS-induced seizure does not induce neural cell death in the hippocampus, it is interesting whether ECS-induced prostanoids by COX-2 activity have neuroprotective effects against seizure.

It is also interesting whether COX-2 products are involved in ECS-induced neurogenesis in the hippocampus. There are several studies on the effects of prostanoids on neurogenesis in the hippocampus. Direct infusion of a stable analog of prostaglandin E2 into the hippocampus increases cell proliferation in the dentate gyrus of the hippocampus and these cells express a neural marker suggesting prostaglandin E2 has stimulatory effects on the hippocampal neurogenesis. Other reports examined the effect of COX-2 inhibitor on ischemia-induced neurogenesis in the dentate gyrus of the hippocampus. Treatment with COX-2 inhibitor after ischemia inhibited enhancement of neural progenitor proliferation, indicating that COX-2 products play a role in the proliferation of neural cells after ischemia. It will be examined whether prostanoids are involved in ECS- or chemical antidepressant-induced neurogenesis.

Recently, research has focused on the roles of inflammatory cytokines such as interleukin-1β (IL-1β) in stress responses and the etiology of depression. It is also well known that prostaglandins, such as E2 type, modulate production of IL-1β in various types of cells including microglia. Future studies will pay attention to relations among prostanoids, inflammatory cytokines, and mechanisms of depression.

5. MOLECULAR AND CELLULAR CHANGES BY ECS IN OTHER BRAIN REGIONS

ECS stimuli can induce molecular and cellular changes in many brain regions other than hippocampus. For example, ECS treatment increases cell proliferation in prefrontal cortex, amygdala, and hypothalamus. In rat prefrontal cortex, chronic ECS treatment increases the number of newly divided cells and these cells express markers of either endothelial cells or oligodendrocytes, but not neurons. In rat hypothalamus, chronic ECS treatment induces an increase in endothelial cell proliferation in specific areas such as paraventricular nucleus and ventromedial hypothalamic nucleus. In rat amygdala, chronic ECS stimulates cell proliferation in the four main nuclei; a majority of the cells proliferating in response to ECS are glial cells expressing the oligodendrocytes progenitor marker. These results suggest that ECS treatment activates many brain regions. Indeed, it has been reported that a single ECS transiently increases c-fos expression in the hippocampus, prefrontal cortex, hypothalamus, and amygdala, indicating that ECS induces neuronal activation in many areas. Upregulation of glia and endothelial cells in response to ECS could serve to reverse the atrophy and loss of cells that has been observed in depressed patients. In addition, induction of endothelial cells by ECS could indicate that there are changes in blood vessel structure and integrity that could contribute to the actions of ECS. Additional studies are needed to identify mediators responsible for ECS-induced cell proliferation and to characterize their function in models of depression.

ECS treatment also affects gene expression pattern in many brain regions. Conti et al. examined transcriptional changes induced by ECS as a fast-onset treatment in seven different brain regions and compared them with those induced by fluoxetine as a typical slow-onset SSRI treatment. Two-day ECS treatment strongly affected the locus coeruleus, indicating that fast-onset ECS action is associated with “activation” of brain regions containing noradrenergic neurons. On the other hand, the effects of 14-d SSRI treatment were primarily in the dorsal raphe and hypothalamus.

As mentioned above, studies have shown that ECS induces changes of gene expression pattern in many different brain regions, but there are many questions that need to be addressed. For example, are there interactions in ECS-induced transcriptional changes among different brain regions? Studies to identify the transcriptional changes in different regions and to analyze these changes using bioinformatics approach are needed. In addition, functional analysis is also important.
to identify the roles of these gene products in antidepressant actions. Region-specific approaches are needed further to analyze the role of specific gene products in different regions.

6. BEHAVIORAL EFFECTS OF ECS TREATMENT IN RODENT MODELS

The forced swim test is the most widely used animal model in depression research. Although an acute treatment with ECS did not reduce the duration of immobility in the forced swim test of rats, chronic treatment with ECS significantly reduced immobility time. In the tail suspension test in mice, chronic ECS for 14 d showed a reduction of immobility. Furthermore, ECS can abolish behavioral effects of chronic stress on the forced swim test. One study showed that daily restraint stress for 21 d displayed higher increases of immobility in the forced swim test whereas ECS protected against the deleterious effects of the stress paradigm. Another study showed that ECS treatment for 6 d decreased immobility time in tricyclic antidepressant-resistant depressive model of rats. This result suggests that ECS shows antidepressant-like action via different mechanisms from chemical antidepressant pathway.

However, the behavioral analysis in the ECS model is insufficient to understand clinical efficacy. Recently, several behavioral paradigms that are dependent on long-term antidepressant administration were established. One example is novelty-suppressed feeding; another is chronic unpredictable stress-induced behavioral changes. Behavioral comparison between ECS and chemical antidepressants on these paradigms will help to identify similarities and differences of these treatments. Especially, it is important to identify the neural circuit and the molecular pathway to mediate the behavioral changes by ECS so as to find novel targets for antidepressants.

7. SUMMARY AND CONCLUSION

Here, I described the molecular, cellular, and behavioral effects of ECS. In the dentate gyrus of the hippocampus, ECS treatment regulates gene expression and increases neurogenesis. Among genes regulated by ECS, neurotrophic/growth factors and neuropeptides including BDNF, VEGF, and VGF are especially noticeable, because they showed both antidepressant-like and neurogenic effects. I also focused on the role of COX-2 in the hippocampus, because induction of this gene by ECS is very strong in the hippocampus. It has been suggested that COX-2-derived products, prostanoids, function in memory formation, neuroprotection, and neurogenesis in the hippocampus. The relation between the role of COX-2 and antidepressant effects of ECS is an interesting question. Chronic ECS treatment also induces morphological and electrophysiological changes in mature granule neurons of the dentate gyrus in the hippocampus, and increases glial and endothelial proliferation in several brain regions including prefrontal cortex, hypothalamus, and amygdala. The contribution of these cellular changes to anti-stress and antidepressive effects will be addressed in future. At this point, behavioral analysis in ECS treatment is insufficient to understand clinical efficacy. It is important to identify the neural circuit and the molecular pathway to mediate the behavioral changes by ECS. To identify the roles for molecular, cellular, and behavioral effects on the action of ECS will provide new insights to find potential targets for novel antidepressant drug design.

Acknowledgement I am grateful to Drs. Atsushi Ichikawa, Shuh Narumiya, Yukihiko Sugimoto, Ronald Duman, and Yasushi Okuno for their encouragement and criticism. I also thank Dr. Tomoyuki Furuyashiki, Ms. Mari Sakaia, Mr. Yuhki Imoto, and Ms. Mamiko Sukeno for daily discussions.

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