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Multi-target Therapy for Subcellular Incompatibility in Brain Disorders

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Abstract

Most brain disorders are caused by a number of pathogenic factors, which lead to the pathological impairment in subcellular organelles and compartments. Recent studies indicate that pathological changes in certain brain disorders include the incoordination among different nerve cells and the incompatibility among subcellular compartments. In this regard, therapeutic strategies for these brain disorders are better to act on multiple molecular and cellular targets in order to correct the neuron-specific incoordination and the subcellular incompatibility. The strategy of multi-target therapy is expected to be advanced to that of single-target therapy that leads to long-term drug-resistance or drug-dependence. In this mini-review, we summarize the data about subcellular incompatibility in certain brain disorders (such as epilepsy, anxiety and depression) and propose the therapeutic principle of multiple targets for their treatments.

Introduction

The brain includes the different kinds of neurons and glia cells, which constitute neural networks via synapses. Each of nerve cells consists of different subcellular compartments. The coordination among nerve cells and the compatibility among subcellular compartments are critical for the neuron encoding to manage well-organized cognitions [1-4]. Their incoordination and incompatibility lead to brain disorders [5]. The brain disorder is defined as its dysfunction in the aspects of neurology and psychiatry, e.g., mental retardation, epilepsy, anxiety, depression, schizophrenia and so on. These brain disorders are often caused by multiple pathogenic factors and accompanied by many pathological changes in signal pathways and subcellular compartments. For instance, genetic alternations are associated with epilepsy, depression and schizophrenia [6-11]. Abnormalities in signal molecular pathways are observed in depression and schizophrenia [12-16]. These molecular alternations induce neuron atrophy and synapse dysfunction in many brain regions through impairing subcellular organelles, leading to major depression, schizophrenia and mental illness [17-26]. In these regards, therapeutic strategies to such brain disorders should be to correct the abnormality in multiple genes, signal molecules and subcellular organelles. Recent reports imply that neuronal incoordination and subcellular incompatibility are associated with certain brain disorders. The incompatibility among subcellular compartments occurs in epilepsy and depression [27,28]. The incoordination in excitatory versus inhibitory synapses is associated to epilepsy, anxiety and depression [4,29,30]. Therefore, the corrections of the neuronal incoordination and subcellular incompatibility should be also considered in multi-target therapy. In this mini-review, we will summarize the pathological characteristics of neuronal incoordination and subcellular incompatibility in some brain disorders as well as propose their therapeutic strategies.

Neuronal Incoordination in Epilepsy

It is suggested that the coordination between excitatory and inhibitory neurons as well as the compatibility among subcellular compartments in the cerebral cortices may grant endogenous mechanisms for seizure self-termination [5], such as function compatibility between presynaptic and postsynaptic partners and activity-induced spontaneous spikes [4,31,32]. The neuronal incoordination and subcellular incompatibility lead to the synchronous discharges in a population of excitatory neurons, i.e., seizure activity for epilepsy. The compatibility should be maintained in the divergence units, in which each neuron in the brain sprouts many axon branches that innervate their correspondent target neurons. Axonal branches from this neuron propagate somatic spikes to drive their diversified postsynaptic neurons [33,34]. The activity diversities of postsynaptic neurons require the functional states of their presynaptic axon branches to be differentiated in order to constitute the compatible partnership between presynaptic axon branches and postsynaptic neurons, i.e., a functional compatibility between presynaptic and postsynaptic partners. In other words, each neuron uses its axon branches as the fractional diverters to regulate its postsynaptic neurons appropriately. This hypothesis has been examined by a current report [4]. The axon branches from a neuron propagate its somatic spikes, in which their frequencies are differentially weakened due to propagation failure. Their innervated postsynaptic partners produce spikes with different abilities. The presynaptic axon branches with high spike propagation ability innervate the postsynaptic neurons with the high spike production ability, or vice versa (Figure 1). The spiking ability between presynaptic and postsynaptic partners is linearly correlated. Moreover, the release probability of presynaptic transmitter is linearly correlated with the sensitivity of postsynaptic receptors [4]. Thus, there is the functional compatibility between presynaptic and postsynaptic partners. In terms of physiological impact, postsynaptic neurons may set spike ability in their presynaptic axon branches making themselves be activated properly. Their compatibility prevents the situations that active axons act onto inactive neurons leading to ineffective energy-cost as well as inactive axons cannot drive active postsynaptic neurons to form the silent partner. These situations lead to seizure discharges in a population of neurons [4,5]. A therapeutic strategy to arrest seizures is to rebalance the functional compatibility between presynaptic and postsynaptic partners.

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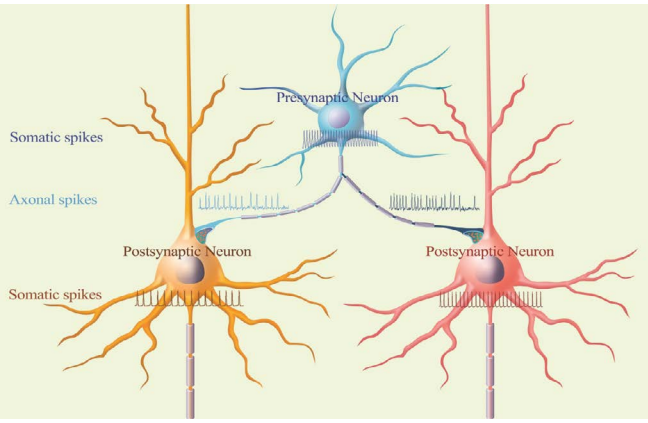

Figure 1: The functional compatibility between presynaptic axon branches and postsynaptic nerve cells. A neuron sprouts axon branches to innervate the different postsynaptic neurons. Somatic sequential spikes in this presynaptic neuron (blue) are propagated to its branches (blue versus dark-blue), where the spikes are propagated differently. The axon with a high ability of propagating spikes (dark-blue) terminates onto the postsynaptic neuron with a high ability of producing somatic spikes (red). The axon with a low ability of propagating spikes (blue) terminates onto the postsynaptic neuron with a low ability of firing somatic spikes (orange).

Excitatory neurons and inhibitory neurons interact each other to maintain the balance of neuronal networks [1,5]. The excitatory neurons activate the inhibitory neurons that inhibit the excitatory neurons by feedback and feedforward. When a population of excitatory neurons are overly active, their persistent activities are able to induce spontaneous spikes in the inhibitory neurons [31,32]. The activity-induced spontaneous spikes (AISS) will suppress over-excitation in a population of excitatory neurons to terminate seizures. As AISS depends on the activation of voltage-independent sodium channels on the axon of inhibitory interneurons [31], one of the therapeutic strategies to arrest seizure can be done by facilitating the activation of voltage-independent sodium channels. Based on two examples about endogenous mechanisms in different subcellular compartments and neurons for seizure self-termination, the multi-target therapy in neuron-specific manner should be used to treat epilepsy. This strategy is advanced, compared with present antiepileptic medication by strengthening GABAergic synaptic transmission or weakening neuronal action potential [35], in which epileptic patients become insensitive to these medications [36,37]. The mechanisms for this drug-resistance may result from the chronic compensatory change of cellular responsiveness to these drugs. For example, long-term blockade to voltage-gated sodium channels enhances neuronal spiking ability [38]. The long-term use of $GABA_A$ receptor agonists leads to receptor desensitization [39,40]. In addition, the lack of long-term medical effectiveness may result from a fact that these drugs to arrest epilepsy are not neuron-specific. The effects of $GABA_A$R agonists and sodium channel blockers on both excitatory and inhibitory neurons do not alter their relationships to shift hyper-excitation toward hypo-excitation in neural networks.

Subcellular Compartment Incompatibilities in Depression

Major depressive disorder is featured as anhedonia, low self-esteem and suicide. Sustained stress to the genetically susceptible individuals leads to dysfunctions of monoamine, brain-derived neurotrophic factor and hypothalamus-pituitary-adrenal axis [12,41,42], which induce the atrophy of the neurons and synapses in brain reward circuits [19,21]. Because monoamine acts on the presynaptic and postsynaptic membranes of excitatory synapses to potentiate their signal transmission [43], these pathological alternations are expected to be improved by raising monoamine in synaptic clefts with serotonin reuptake inhibitor, non-adrenaline reuptake inhibitor or monoamine oxidase inhibitor [17,44]. However, the response of depression patients to this therapy shows the delayed onset for weeks [45]. Other pathological mechanisms and therapies need to be elucidated. Recent data indicate that major depression subjects possess the decreased density of GABAergic neurons in the prefrontal cortices [46-48] and the lowered tone of GABAergic transmission in the brain [49,50]. Such changes may be caused by chronic stress. For instance, stress hormones affect the function of $GABA_A$ receptors [51,52] and reduce the density of GABA receptors [53,54]. $GABA_A$ receptor enhancers are used to be antidepressants, however, there is controversy in therapeutic outcome [55-57]. To this issue, we hypothesize that there are incompatible changes in the sub-compartments of GABAergic neurons and synapses, e.g., presynaptic GABA release versus postsynaptic GABA receptors and the outputs of GABAergic neurons versus their reception from excitatory inputs.

Our study indicates that the output and excitability of GABAergic neurons in the prelimbic cortex from depression-like mice decrease and that their reception from glutamatergic inputs rises [28]. These decreased outputs and increased receptions in GABAergic neurons may result from that stress-induced primary dysfunction in GABAergic neurons initiates unknown mechanism to enhance their sensitivity and reception from excitatory input, a compensatory process among subcellular compartments for neuron survival [3]. The decreased presynaptic GABA releases and the increased postsynaptic $GABA_A$-receptor responses indicate a homeostasis within GABAergic synapses [28], which explains a controversy in the use of GABA-receptor enhancers as antidepressant [58]. The compensatory changes among subcellular compartments tend to maintain functional homeostasis in these GABAergic neurons and synapses. On the other hand, the incompatibilities among subcellular compartments as well as between presynaptic and postsynaptic partners may result in neuronal interaction and synaptic transmission to be inefficient, which constitute neural substrates for depressive disorder. The rebalance of their compatibility should be considered as one of therapeutic strategies, since the coordination and compatibility among subcellular compartments are present under the physiological conditions [3,4]. Testable strategies for major depression treatment are given in Figure 2.

Subcellular Compartment Incompatibility in Anxiety

Anxiety is characterized as unstable mood, negative interpretation and social phobia. The defect of many genes is presumably associated with anxiety [59-61], which leads to pathological changes in serotonergic, GABAergic and glutamatergic synapses in the limbic system [29,62-65]. Selective serotonin reuptake inhibitors or GABA receptor enhancers have been used to treat anxiety [66,67]. Their effectiveness remains to be reevaluated due to drug resistance and unfavorable side-effects [68-71]. Therefore, multi-target therapy is expected to be used to treat anxiety. The incompatibility has also been observed in excitatory synapses and inhibitory synapses on the glutamatergic neurons in the prefrontal cortex from anxiety mice. For instance, the decreased probability of GABA release from presynaptic inhibitory neurons is associated with no change in the sensitivity of $GABA_A$ receptor in postsynaptic neurons [65]. The increased efficacy of excitatory synapses is associated with the decreased density of excitatory synapses on glutamatergic neurons

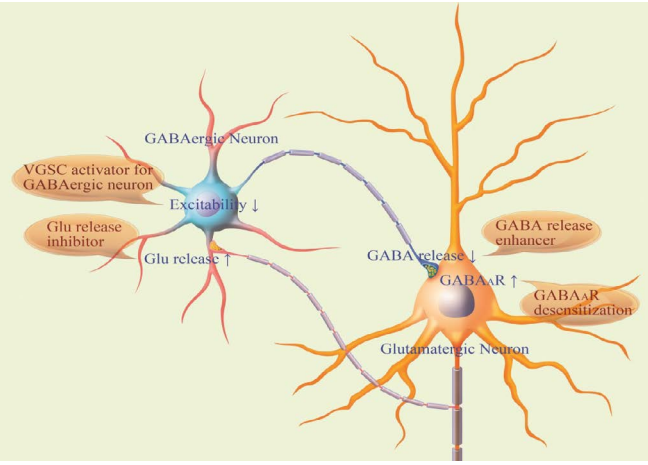

Figure 2: Pathophysiology in prelimbic cortical GABAergic and glutamatergic cells from depression mice and therapeutic strategies. The excitability of GABAergic neurons and the release of their axonal GABA decrease. Their reception from glutamate (Glu) release and innervation from glutamatergic neurons rise. The incompatibility among the subcellular compartments of GABAergic neurons reduces their efficiency to coordinate their downstream nerve cells. In glutamatergic neurons, their responses to GABAergic input increase. These alternations impair the interaction between GABAergic and glutamatergic neurons. The therapeutic strategies stated in shadow symbols will be to reduce Glu release from excitatory neuron and GABAAR responsiveness in excitatory neuron as well as to elevate GABA release from inhibitory neuron and voltage-gated sodium channel (VGSC) activity in inhibitory neuron.

[29]. In spite of this compensatory homeostasis at the excitatory and inhibitory synapses, the incompatibilities between presynaptic and postsynaptic compartments or between synaptic efficacy and synapse density lead to inefficient functions at these synapses. The rebalance of subcellular compartment compatibility at these synapses should also be an ideal strategy for anxiety treatment.

Conclusions

Based on these data, the brain disorders, such as epilepsy, depression and anxiety, are caused by many genes and signal molecules, and are accompanied by incompatibility among different subcellular compartments. The strategies of multi-target therapies are required for their treatments, but the medications for these brain disorders are variable since their pathological changes are different. With this strategy, the dosages of multiple drugs can be reduced to prevent drug resistance, dependence and side-effects. Whether multi-target strategy is used to treat other neurological and psychiatric disorders should also be considered once they are proved to be caused by the dysregulation of multiple molecules and the incompatibility among subcellular compartments. It should be pointed out that the correct diagnosis of the brain disorders is important for the proposed therapies and that their effectiveness and duration need to be evaluated in terms of the variability of individual patients in their responses to multi-target therapies, i.e., the combination of personalized medicine (or precise medicine) and multi-target therapy.

It is noteworthy that the medications in traditional Chinese medicine [72] are similar to this multi-target therapy, in which each of the herbs presumably plays major or minor roles in treating the given diseases. Numerous natural compounds included in herbs act to different targets, such as receptors, enzymes and signal pathways. However, their targets remain unclear. A combination of this multi-target strategy with the compounds whose action targets are precisely defined should shed light on future direction for the therapy of various diseases. The therapeutics of brain disorders will be benefited from developing the compounds with precise targets and the strategies for their combined usage based on the multiple pathogenic factors and pathological alternations in subcellular incompatibility.

Competing Interests

Jin-Hui Wang and Shan Cui declare no competing interests.

Author Contributions

JHW contributes to writing, and SC contributes to figure.

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