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Study of Phosphorylation of Gabaar Levels in Cell Line of Neuroblastoma with Knocked Down Malic Enzyme 2 (Me2)

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Abstract

Malic enzymes (ME; EC 1.1.1.40) represent a family of oxidative decarboxylases that catalyze the divalent metal ion (Mn^{2+} or Mg^{2+}) dependent irreversible oxidative decarboxylation of L-malate to yield CO2 and pyruvate, with concomitant reduction of dinucleotide cofactor NAD^+ or $NADP^+$. In neurons pyruvate produced from malate is a substrate for the neuronal synthesis of γ-aminobutyric acid (GABA), which is a major inhibitory neurotransmitter in the central nervous system (CNS). It mediates fast synaptic inhibition through GABAA and GABAC ionotropic receptors as well as slow and prolonged synaptic inhibition through the metabotropic GABAB receptor. The GABAA receptor is a ligand-gated ion channel whose function and activity can be regulated by ligand binding or alternatively may be influenced indirectly through the phosphorylation of specific subunits that comprise the GABAA receptor pentamer. AKT phophorylate gamma-aminobutyric acid type A receptor (GABA (A) R), the major inhibitory receptor of fast synaptic transmission in the brain of mammals. phosphorylation by AKT increase the number of GABA (A) R located in the plasma membrane and subsequently, receptor-mediated synaptic transmission in neurons increases. ME2 deficiency cell lines were created by ACL shRNA lentiviral particles in Iscove's Modified Medium. Immunoblotting showed a decrease in GABA (A) R phosphorylation in down cell line in comparison with the control.

Keywords: *Phosphorylation; $GABA_AR$; Malic enzyme 2 and AKT*

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Introduction

Malic enzymes (ME; EC 1.1.1.40) is a family of decarboxylases oxidative who decarboxylation oxidative non-reversible dependent on metal ions bivalent (Mn^{2+} or Mg^{2+}) L- malate to CO_2 and pyruvate product coincided with a revival of cofactor dinucleotide NAD+ or NADP+ catalyze [1]. In different species, these enzymes exhibit well-preserved sequences and the topology are quite similar, indicating their vital biological functions. Three isoforms malic enzyme in mammals based on the specificity of nucleotide They have been identified: cytosolic dependent on $NADP^+$ (ME1), mitochondrial-dependent NAD^+ (ME2), and malic enzyme mitochondrial-dependent NAD $(P)^+$ (ME3)

is shown That ME2 does not tend to physiologically with NAD^+ cofactor, however, can use NAD^+ and $NADP^+$. Enzymes ME1, ME2 and ME3 important roles in physiological and pathological functions, such as insulin secretion and epithelial- mesenchymal transition (EMT) [3].

The formation of glutamate and GABA transmectors requires interactions between neurons and astrocytes to store and release them. Both these transaminase amino acids in the brain consist of glucose in astrocytes, but not in neurons, because they lack the pyruvate carboxylase (PC) enzyme [6]. Malic enzyme 2 (ME2) is associated with the malate-aspartate shuttle system and plays an important role in the metabolism of glutamine and neurotransmitter gamma-amino-butyric acid (GABA) via NADH and pyrovate products. In the neurons, the pyruvate from malate in the reaction of the enzyme malic, the synthesis substrate is γ-aminobutyric acid [7,8].

A glucose molecule metabolized by glycolysis in cytosol is converted into two precursor molecules in a precise, complex pathway. In neurons and astrocytes, pyroate metabolism through acetyl coenzyme A (ac.CoA) leads to the production of citrate in the tricarboxylic acid (TCA) cycle by the agglomeration of the precursor activated oxalostat (OAA) from the previous cycle. Oxidation of citrate in the TCA cycle involves two decarboxylation, resulting in the production of oxalostat, ready for the next round of cycles, and the reduction of NAD^+ to NADH (and FAD to $FADH_2$), resulting in the production of high levels of energy (ATP) through redox in the transmission chain Electron becomes. Pyruvate decarboxylation, which is active in astrocyte, but not in neurons, produces a new oxalostat molecule, which is subsequently condensed with acetyl coenzyme A, forming citrate, which in the TCA cycle to α-ketoglutarate (α-KG) Metabolized, which can leave the cycle in the form of glutamate (Glu), and catalyzed by aspartate aminotransferase (AAT).

In the cell, the activity of the pyruvate carboxylase and pyruvate dehydrogenase enzymes leads to the production of a “new” citrate molecule. The α-ketoglutarate (α-KG) molecule derived from citrate is extracted from the mitochondrial membrane and the TCA cycle leaves the astrocyte and is formed by transesterification of aspartate and glutamate. At the same time, oxalovate (OAA) is formed from aspartate. The mitochondrial excretion of the α-KG molecule occurs through the α-ketoglutarate/malate exchanger, which is commonly expressed in astrocytes. Cytosolic molasses are produced by the reversal of oxalostatic acid produced by aspartate. Glutamate is also bound to glutamine, and is transmitted to glutaminergic neurons. The formation of glutamate from α-KG is associated with aspartate transamination. In neurons, glutamine converts to glutamate over complex pathways, and is accumulated in vesicles and released in the form of glutamate. Glutamate reabsorption and its oxidative metabolism occur in astrocyte. Cytosolic glutamate is transmitted back to the mitochondria via the aspartate-glutamate exchanger (AGC1), and the mitochondrial aspartate produced from OAA is transmitted to α-KG via trans-ammonation of glutamate to the cytosol [9].

Gamma-aminobutyric acid (GABA) is a major inhibitor of neurotransmitter in the central nervous system (CNS), which is made by GABA axicon terminals and released into the synapse [10]. GABA (γ-amino-butyric acid) was identified in the brain in 1950 and is known as the main inhibitory neurotransmitter in the brain [11-15]. GABA is derived from glutamate, which is a stimulant neurotransmitter itself [16]. The conversion of glutamic acid to γ-amino-butyric acid (GABA) is catalyzed by glutamic acid decarboxylase (GAD), a cytoplasmic enzyme. This enzyme is mainly expressed in gobarergic neurons in the central nervous system as well as in the β-pancreatic cells [17-19]. Glutamate (Glu) is removed by astrocytes and transmitted to pre-synaptic neurons after becoming glutamine (Gln). In stimulating neurons, glutamine is converted to glutamate and re-packaged in vesicles. Like glutamate, GABA is removed by astrocytes and transmitted to pre-synaptic neurons after becoming glutamine. In inhibitory neurons, glutamine is converted to glutamate and then into GABA and packaged in synaptic vesicles [20].

Among the ionic channels in the brain, is the GABA receptor channel. GABA mediates fast synaptic inhibition by connecting to the ionotropic receptors of GABAA and GABAC, as well as latency inhibition by binding to the metabototropic GABAB receptor. GABAB receptor antagonist pre-synaptic neurotransmitter release and post-synaptic inhibitor mediates neuronal excitability [6]. GABA can be connected to metabotrophic GABAB receptors [21-25] or to ionotropic GABAA or GABAC receptors. The activation of the GABAB receptor after synaptic increases the permeability of the membrane relative to K^+ and causes prolonged neural hyperplanation. The activation of GABAB receptors reduces the pre-synaptic transmission of Ca^{++} and the release of neurotransmitters. The activation of ionotropic

GABAA or GABAC receptors, in turn, permeates chloride and bicarbonate ions [26]. The activation of GABAA or GABAC receptors results in the introduction of Cl- and subsequently the creation of an electrochemical gradient, resulting in neuronal hyperplasia. The GABAA receptor is a pentameric channel composed of a combination of subunits, with pharmacological properties, position and kinetics. In mammals, GABAA receptor subunits are known (α1-α6, β1-β, γ1-γ3, δ, ε, and θ), which form a ligated ionized channel complex [27]. 19 genes are involved in the coding of various subunits, GABAA receptors. A number of GABAAR mutations have been associated with epilepsy, including subunit genes α1, γ2, and δ (GABRA1, GABRG2, and GABRD). Each of these mutations has been shown to reduce GABA inhibition and hence the excitability of neurons. GABAA receptors, which interfere with GABAA synaptic inhibition, are the drugs used to treat seizures, including benzodiazepines or barbiturates [28]. The GABA binding opens the chamber (Cl-) receptor channel at two locations of the GABA, located between sub-units α and β. Benzodiazepines are attached to the position located between the sub units α and γ2. Barbiturates, alcohol, and neurosteroids are attached to sites located interspersed with the membranes of the subunits [29].

The GABAB receptor belongs to the G-protein coupled receptor class (GPCRs), with other methotropic glutamate receptors (mGlu), an extracellular Ca^{2+} sensor, and some taste pheromones. Each of these receptors consists of an extracellular domain derived from the Venus flytrap domain (VFT), which agonists attach to it, and a heptahelical domain (HD), responsible for detecting and activating the heterotrimer G protein Is, is. Sensor receptors are Ca^{2+}, mGluRs, and homodimers, the GABAB receptor is a heterodimer consisting of two subunits of homology GABAB1 and GABAB2. Domain N-terminal VFT the GABAB1 subunit is responsible for binding to the ligand, while the dominant VFT of the GABAB2 receptor is not known to bind to the ligand. The component of PAMs binds to the domains of trans-membranes of GABAB2 to enhance the agonist effect. GABAB receptor interacting proteins interconnect with the GABAB receptor C-terminus. GABAB receptor heterodimerization is a precondition for GABAB receptor function. The VFT domain of the GABAB1 receptor is sufficient to connect the ligand, but its association with GABAB2 increases the tendency of the GABAB1 receptor to agonist. Although GABAB2 does not appear to bind to the natural ligand. The GABAB1 receptor requires GABAB2 to reach the cell surface. The connection between the agonist and the VMP receiver of the GABAB1 domains is responsible for changing the position associated with the two domains of VFT and HD. This move allows the activation of G proteins by mediating HD domains and GABAB2.

Protein phosphorylation plays a crucial role in synaptic plasticity, learning and memory in vertebrates. In protein kinase regulated by an extracellular signal of 2/1 (ERK1/2), as well as mitogen activation protein (MAPK), the messenger cascade plays important roles in strengthening long-term regulation in the CA1 region of the hippocampus and for Different forms of learning and memory are essential. Recently, it has been shown that phosphorylation of ERK1/2 is induced by the GABAB receptor in CA1 region of the hippocampus of the mouse. The ERK1/2 messenger ERP1 messenger configuration is extremely complex and specific to the cell type, and the mechanism of ERC1/2 phosphorylation by the GABAB receiver has been partially recognized. Additionally, GABAB receptors bind to copy factors of 2 CREB2 (cAMP-2 responsive element-binding protein)/ATF4 (Doping Activator Factor 4) during spiral-spiral interactions. The activation of the GABAB receptor induces the phosphorylation of ERK1/2 by the CREB phosphorylation intermediary. This effect of the GABAB receptor occurs with Gi/o proteins by releasing Gβγ subunits. [30, 31]

Material and Methods

Cell Culture

Cell culture of the cell line was obtained from the American Type Culture Collection at Iscove's Modified Medium. All environments were placed on calf embryo (10% v/v), 100 units of penicillin and 100 mg/ml streptomycyne, and grown at 37uC and 5% CO_2. Infected cells with shRNA virus were selected with poromycin 1.0 mg/ml, and the ME2 or ACL stack was used for analysis.

Generation of ME2 deficiency cell lines

The cells were transduced separately with shRNA vector control. Three different ME2 and an ACL shRNA fragment were previously determined [32]. Donated cells of lentiviral shRNA ATP citrate lysis (ACL) were used as positive control. Three sequences of shRNA (sans) ME2 used in study

59-CGGCATATTAGTGACAGTGTT-39; shME2-2,
59-CCCAGTATGGACACATCTTT A-39; and shME2-3,
59-GCACGGCTGAAGAA GCATAT A-39
59-GCCTCTTCAATTTCTACGAG- GACTT-39

The production of recombinant portions of lentiviral particles of subconfluent 293FT cells with 3 mg of shRNA plasmid and 9 mg of virapower packaging mix (Invitrogen) used in lipofectamine 2000 (Invitrogen) were co-transfected. Used in lipofectamine 2000 (nvitrogen). After 16h, the culture medium was regenerated and incubated for 48h. The conditioned cultured cells of the lentiveral particles were collected and frozen. Cells of cells with supernatant-bearing porcine enzymes were incubated for 24h. These cells were selected with poromycin (Sigma Aldrich) to create a single vector shRNA encoding constant vector cell line, ME2 shRNA or shRNA ACL. Then clones of pLKO, shME2-1, shME2-2, shME2-3 and shACL were named. In order to produce the ME2 Clone Nucleus, the cells were diluted from Knock Down clones serially in 96 well plates. This single clone was identified by clones of pLKO-s, shME2-1s, shME2-2s and shME2-3s [33].

Western Blotting

- Mechanical digestion of isolated tissues and addition of cold buffer lysis (Invitrogen, UK)
- Sample homogenization and centrifugation at 110g for 30 minutes at 4°C
- Removal of the supernatant and transferring it to the microtib

Quantitative analysis of the protein content of tissue extracts by the Bradford method was used to draw the standard Bradford standard of BSA as a standard protein. Finally, using the linear equation obtained from the standard chart and also the absorbances obtained from different extracts, the concentration The protein is calculated in milligrams per ml.

- SDS-PAGE and western blot electrophoresis: After the Bradford test, 34 micrograms of each protein sample are mixed and used in a 1:1 sample with a sample buffer. The molecular weight marker is used to determine the protein's position. Also, the β-actin antibody is used to load control. After electrophoresis to transfer proteins from gel to membrane, the sandwich model is prepared by Watten sheets, nitrocellulose membranes and gel and placed in a transfer tank containing a transfer buffer. After blocking by 5 ml of 3% BSA blocker solution and washing with Trison buffer solution containing Tween membrane for 1 hour with 2 ml of primary antibody diluted in BSA 3% from 1 to 1000 and then It is incubated for 30 minutes in a secondary antibody (ABC Staining Kits) with a concentration of 1.000 in PBS/BSA. The filter is then exposed to the ABC-AP reagent (Vector Laboratories) for 30 minutes. Finally, the Vector Blue-Alkaline Phosphatase Substrate solution is poured onto the filter. After the appearance of blue protein bands, the substrate solution is removed and the filter is washed. Finally, after membrane drying, it is captured by the camera (japan) canon g 11. Finally, Image J will be used for the densities of the bands.

Results

Immunoblotting indicated a decrease in the amount of GABA (A) R phosphoryl in the cancerous cells compared to control.

Discussion

GABAA receptor activity and activity as a ligated ion channel can be regulated by ligand binding or may indirectly be indirectly affected by phosphorylation under the constituent units of the pentamer receptor of GABAA. The agreed position of the extracellular-signal regulated kinase (ERK), the main vector of the MAPK pathway, is the alpha-subunit of the GABAA receptor. The ERK/MAPK pathway (MAPK-activated protein kinase, MAPK) initiated by Raf is a serine/threonine kinase, which is itself phosphorylated by the MEK. The ERK/MAPK kinase pathway plays a role in regulating cell survival, as well as synaptic plasticity and memory. The objectives and mechanisms that are regulated by the ERK/MAPK pathway and related processes are diverse, and may include phosphorylation of nuclear factors such as Elk-1 and CREB, whose activation would result in the regulation of gene transcription, And phosphorylation

of various cytoskeletal elements, such as proteins with microtubules (MAP-1, MAP-2, MAP-4) and tau. The ERK/MAPK route can also target ion channels, thus affecting their functional characteristics [34]

The AKT protein *in vitro* and *in vitro*, the receptor of type A gamma-amino-butyric acid (GABA (A) R), the primary receptor of phosphorylation of fast-release fasting of synaptic transmission in mammalian brain. AKT-induced phosphorylation increases the number of GABA (A) Rs located on the surface of the plasma membrane and subsequently the transfer of receptor-synaptic transmission in neurons. The AKT protein, also called the protein kinase B (PKB), is a serine/threonine kinase involved in a variety of signal transduction pathways, which are mainly expressed in the brain. The AKT protein is an apoptotic action and is therefore vital in neuronal survival. At the same time, the potential role of dynamical dynamics of synaptic transmission is also known [35]. Methane ME2 induces death and cellular differentiation *in vitro* and affects the PI3K/ AKT/mTOR pathway. The NE2 ME2 inhibits AKT activity in the cells [36].

Conclusion

The strong evidence suggests that malic enzyme (ME2) is a predisposing gene for generalized idiopathic epilepsy (IGE). The study shows that the mutation of the recessive gene of ME2 has a serious effect on IGE syndromes [37]. Epilepsy A common term involves multiple syndromes, with symptoms, etiology, prognosis, and treatment [38]. Epilepsy, which is characterized by seizures, may be a sign of many neurological disorders and can often not be defined in the etiology. In a significant number of patients with epilepsy, the etiology of epileptic seizures is not known [39]. Epilepsy A common term involving multiple syndromes, with symptoms, etiology, prognosis, and treatment is different. The role of GABAA receptors in pathophysiology of epilepsy has been experimentally investigated in most cases in temporal lobe epilepsy (TLE) [40]. Epilepsy is characterized by high and uncontrolled activity, or all central nervous system.

Animal studies indicate that the seizure is due to the fluctuation of the thalamic lattice neurons (which are inhibitors of gamma-amino-butyric acid production neurons), and the thalamus-cortesis and cortex-thalamus stimulatory neurons [41].

Due to neuropsychological and biological complications of uncontrollable seizures and heavy costs of anticonvulsants, especially new drugs and their complications, it is necessary to consider simple, non-invasive and sensitive methods for the treatment of epilepsy resistant to medical treatment. To be placed. Hence, it seems that by investigating the effect of Nitrine -1 as an effective compound on growth and differentiation of neurons, it can be identified as an agent in the repair of GABA receptors in brain neurons involved in epilepsy.

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