From the camp pathway to search the ketamine-related learning and memory

S. PENG1,2, X. YANG3, G.-J. LIU3, X.-Q. ZHANG1, G.-L. WANG3, H.-Y. SUN3

Abstract. – Protein kinase A (PKA) phosphophylates and activates cAMP response element-binding protein (CREB), which then binds to CRE domain on DNA and in turn activates genes involved in the process of learning and memorization. It has been demonstrated that CREB is involved in the learning and memory deficits that are caused by ketamine.

In this review, we attempt to discuss the role of ketamine and cAMP pathway and relevant regulatory protein ERK in learning and memory through the molecular mechanism and signaling pathways. In this review, we also try to find a new way to treat the impairment in learning and memory induced by ketamine.

Key Words: Ketamine, Cyclic AMP, cAMP response element-binding protein, Extracellular signal regulating kinase, Phosphodiesterase 4, Learning and memory.

Introduction

Among the pediatric clinical anesthesia, ketamine is one of the most commonly used medicines. The researches of its impact on learning and memory have always been a clinical concern. In this article, we are going to explore the formation of learning and memory impairment caused by ketamine.

Materials and Methods

Ketamine's Impact on Learning and Memory

N-methyl-D-aspartate (NMDA) receptor, located in hippocampus, plays an important role in the induction, maintenance, and expression of the long-term potentiation (LTP) that mediate the process of learning and memory. Ketamine is a non-competitive antagonist of NMDA receptor. Studies have shown that repeated injection of ketamine to rats after surgery can significantly decrease both NMDA and its receptors quantity within the hippocampus. It is also found that intraperitoneal injection of ketamine can damage the space exploring and learning ability of 21-day-old SD rats. Moreover, this damage to learning and memory function in neonatal rats caused by ketamine is sustainable to adult, which can not be repaired or restored with the development of the central nervous system.

Impact of cAMP pathway and its Regulatory Proteins ERK on Learning and Memory

cAMP Pathway

Cyclic adenosine monophosphate (cAMP) pathway plays a very important role in learning and memory. cAMP can activate protein kinase A (PKA) and C (PKC) subunit to enter in the nucleus, which make the CREB transcription factor phosphorylated on specific serine stump and it becomes activated. The phosphorylated and activated CREB can combine on CRE near the cAMP regulated target gene on the DNA molecule, regulate gene transcription, and thus synthesize the proteins associated with learning and memory.

Before training the learning and memory behaviour, the injection of CREB antisense oligonucleotide into the rat hippocampus can lead to its spatial learning defects in the Morris water maze. As for the rats with the bilateral fimbria fornix transectioned, the reduced phosphorylation level of the hippocampal CREB can also lead to damage to the avoidance memory. It has also been demonstrated that CREB phosphorylation mediated transcription can also promote the generation of new synaptic links, improve the survival rate of neurons, and alleviate the brain cognitive impairment after injury.

Corresponding Author: Gongjian Liu, MD; e-mail: pengshengtongji@gmail.com
LTP is the main mechanism of the mammalian central nervous system to store information. It is the cellular basis of learning and memory and has become an effective model for neuronal plasticity. A growing number of animal experiments have improved the irreplaceable role of CREB in LTP and memory process mediation. Different protein kinases, including extracellular signal-regulated kinase-2 (ERK2), protein kinase A (PKA), calcium/calmodulin-dependent protein kinase type IV (CaMKIV), etc., can induce or promote LTP through phosphorylated CREB and, therefore, improve the learning and memory function in animals. Montarolo et al. has found for the first time from the Aplysia the long term of cAMP-CREB pathway facilitation activities in the memory process, and has mentioned the first mechanism of learning and memory dependent gene expression. In the studies of vertebrates, Florion et al. has found that through CREB phosphorylation and the activation of intracellular protein kinase cascade, external stimulation triggered effect can induce target cell gene expression to cause a long-range effect on memory and learning.

**cAMP Pathway and ERK Protein**

Extracellular signal-regulated kinase (ERK) is an important serine/threonine protein kinase. Its substrate include transcription factors, histones, other important intracellular kinases and a K+ channel. These substances are the important component within the cells, and are essential in the process of learning and memory formation. The activated ERK can activate CREB through the ribosomal S6 kinase activation, which is acting on the CRE to start the CRE-dependent transcription. In addition, ERK can also phosphorylate directly the transcription factor CREB. Other studies have shown that ERK can also regulate the content of cAMP through the cross-dialogue with phosphodieterase-4 (PDE-4), and form a cAMP/ERK regulatory pathway. The work of Kelly et al. has proved that the MAPK/ERK signaling pathway has been involved in learning and memory consolidation in the hippocampus.

**Impact of Ketamine on Learning and Memory Through cAMP Pathway and its Regulatory Proteins ERK**

**Ketamine and cAMP Pathway**

Experiments have shown that ketamine can temporarily inhibit the hippocampal P-CREB expression so to affect the memory capacity of immature rats. Further studies have confirmed that the cAMP-regulated downstream protein CREB has participated in the formation of ketamine which in turn involved in the learning and memory in immature rats. The low CREB transcription in mice can lead to a significant damage to LTP and the long-term memory, while the high expression of CREB can bring both a significant enhancement of memory and LTP and an obvious improvement in social cognitive function. CREB may participate in the regulation of ketamine formation and learning and memory impairment in immature rats by affecting the role of NMDA receptors. As a double-gated channel of voltage and ligand, NMDA receptors will combine Mg2+ and close in the resting potential. During the postsynaptic membrane depolarization, Mg2+ will be separated from the channel; the binding of neurotransmitter and receptors causes the channel to open, then as second messenger, Ca2+, inter into the cell, activate Ca/CAMK II, cAMP-dependent protein kinase and others, and ultimately start a series of biochemical reactions including CREB transcription and phosphorylation and the formation of LTP.

**Ketamine and ERK Protein**

Studies have confirmed that the ERK signaling transduction pathway has participated in the process of learning and memory. The activation of NMDA receptor is mainly regulated by A-type potassium channel encoded by the Kv4 family members, and ERK activation can result in the phosphorylation of Kv4-2α subunit, thus a decline of the A-type potassium current, and induce the amplification of action potentials, enhance the dendritic membrane excitability and, therefore, induce the formation of LTP. Ketamine may affect learning and memory through its inhibition of ERK signaling transduction pathway.

**Results**

**PDE-4**

Latest research showed that cAMP-specific hydrolase inhibitors can reverse the damage of learning and memory. Phosphodiesterase-4 (PDE-4) is a cAMP specific hydrolytic enzyme and its hydrolyzation can decrease cAMP levels. Through the regulation of signaling pathways of cAMP/PKA/CREB and others, it will affect the intracellular CREB regulatory gene expression, so
that the part of protein involved in learning and memory might not be synthesized and, thereby, interfere the long-term formation of memory. By increasing the cAMP levels by the cAMP-specific hydrolytic enzyme PDE-4, Vecsey et al. have reversed the memory loss in rats caused by sleep deprivation. Previous work have also demonstrated that the rats will significantly lose their memories after being administered NMDA receptor inhibitor MK801, and re-injection of PDE-4 inhibitor can reverse this forgetting effect. Moreover, the administration of muscarinic M receptor agonist, scopolamine, can cause the impairment of working memory and reference memory, and these two kinds of memory impairment can be reversed by the application of PDE-4 inhibitor. It is then speculated that these effects may be related to the PDE-4 inhibitor, which has increased hippocampal cAMP level and hippocampal neurons LTP, and has changed hippocampus synaptic plasticity.

In summary, ketamine affects learning and memory through cAMP pathway and relevant regulatory proteins ERK. At the same time, in order to search their molecular mechanisms and signal transduction pathways, we need to continue exploring and screening new effective medicine to prevent ketamine caused postoperative learning and memory impairment.

Conclusions

The impact and mechanisms of CAMP/PKA/CREB signaling pathway and related regulatory proteins PDE-4 and ERK on learning and memory has achieved remarkable results. By combining these approaches, it is possible to provide a new therapeutic approach for clinical treatment of patients, a new target for new effective drugs, and to prevent postoperative learning and memory dysfunction.

References

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Conflict of Interest

The Authors declare that they have no conflict of interests.


