Review Article

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Effects of Tacrolimus on Cognitive Functions of the Central Nervous System: A Review Article

Z. Salimi (PhD)[1,2], F. Moradpour (PhD)[1,2], F. Zarei (PhD)[1,2], Z. Rashidi (PhD)[1], M. R. Khazaei (PhD)[1], S. M. Ahmadi (PhD)[*1], F. Khazaei (BSc)[3]

1.Fertility and Infertility Research Center, Health Technology Institute, Kermanshah University of Medical Sciences, Kermanshah, I.R.Iran

2.Department of Physiology, Faculty of Medicine, Kermanshah University of Medical Sciences, Kermanshah, I.R.Iran

3.Student Research Committee, Kermanshah University of Medical Sciences, Kermanshah, I.R.Iran

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ABSTRACT

BACKGROUND AND OBJECTIVE: Tacrolimus belongs to the family of calcineurin inhibitors and is extensively used as an immunosuppressive drug after allogeneic organ transplant. According to the inhibitory effects of calcineurin on synaptic plasticity and memory functions, it seems that the administration of tacrolimus leads to changes in the electrophysiological responses and memory functions. Therefore, this article includes studies in which tacrolimus involvement in cognitive functions such as synaptic plasticity, learning and memory are investigated, and the possible mechanism of the effect of tacrolimus on synaptic plasticity and memory are explained.

METHODS: In this narrative review article, we searched PubMed and Google Scholar databases using the keyword "Tacrolimus", "Calcineurin", "Synaptic Plasticity", "Learning", "Memory", and "Free radicals" to provide an overview of effects of tacrolimus on cognitive functions. Finally, articles published on these topics between 1987 and 2021 were investigated.

FINDINGS: Among the 5632 sources found, 72 articles were considered appropriate for the purpose of the research. Findings support that the administration of tacrolimus (TAC) improves cognitive functions such as learning, memory, and synaptic plasticity. Furthermore, TAC has neuroprotective effects against oxidative stress-mediated cognitive dysfunctions.

CONCLUSION: The results of the study showed that TAC may improve learning, memory, and synaptic plasticity, possibly by calcineurin inhibition, reducing the level of free radicals, and altering calcium and glutamate levels.

KEY WORDS: *Tacrolimus, Calcineurin, Synaptic Plasticity, Learning, Memory, Free Radicals*.

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[*]**Corresponding Author: S. M. Ahmadi (PhD)**
Address: Fertility and Infertility Research Center, Kermanshah University of Medical Sciences, Kermanshah, I.R.Iran
Tel: +98 83 34274618
E-mail: mojtabakmahmadi@yahoo.com

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Introduction

Long-term potentiation (LTP) is one of the most noticeable topics in neuroscience, referring to the long-lasting enhancement of synaptic efficacy and considered as a molecular and cellular mechanism of learning and memory (1). It has been well established that various protein kinases and phosphatases are involved in synaptic plasticity, learning and memory formation (2). A potential mechanism regulating neuroplasticity and synaptic plasticity is the balance between phosphorylation and dephosphorylation of various substrates by protein kinases and phosphatases (2, 3). The importance of protein kinases in learning and memory promotion has long been recognized. However, the roles of phosphatases in learning and memory suppression are currently being investigated. CaN is the only serine/threonine protein phosphatase under the regulation of calcium/calmodulin that exists at high levels in the hippocampus (4, 5).

A number of studies reported that CaN has an inhibitory impact on hippocampal-based learning, memory, and synaptic plasticity. Reports show that up-regulation of CaN has negative relationships with cognitive functions, while downregulation of CaN improves learning and memory (7, 8). TAC or FK506 is a fungal-derived agent synthesized from streptomyces tsukubaensis bacterium (9). It was first introduced by Tanaka in 1990 (10) and then large number of derivatives, and analogues of this drug were discovered by other researchers (11). This drug has ubiquitous immunosuppressing effects and specifically block the phosphatase activity of CaN. TAC exerts its inhibitory effect on CaN by binding to the protein domain of FK-binding proteins (FKBP) (12). It is usually prescribed more than cyclosporine because it shows better immunity, which is associated with increased survival in patients (13). Interestingly, tacrolimus has good tolerance among children and adolescents (14, 15).

In clinical practice, TAC is extensively used after allogeneic organ transplant for decrease the risk of organ rejection (10, 16). Therefore, understanding the effects of TAC administration on the central nervous system (CNS) is very important. Overall, it seems that the administration of TAC may lead to changes in different cognitive functions, such as learning, memory, and synaptic plasticity. Thus, the present review article primarily aims at investigating the effects of TAC on cognitive functions and determining the possible mechanisms responsible for such effects.

Methods

This narrative review article was approved by the ethics committee of Kermanshah University of Medical Sciences with the code IR.KUMS.REC.1400.111. We searched Google Scholar and PubMed databases using the keywords “Tacrolimus”, “Calcineurin”, “Synaptic Plasticity”, “Learning”, “Memory”, and “Free radicals”. Finally, articles published on these topics between 1987 and 2021 were investigated. After screening the articles published based on the title and abstract of the article, duplicate cases, and articles that were not appropriate for the purpose of this study were removed.

Results

Among the 5632 articles found, after initial review and removal of unrelated studies, 72 articles were finally considered appropriate for the purpose of the paper (Fig. 1).

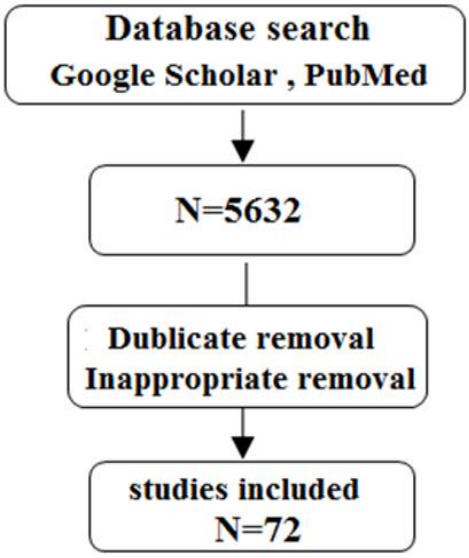

Figure 1. The literature research strategy

Effects of TAC on Synaptic plasticity: hippocampus is one of the most important structures that mediates cognitive functions and behaviors. LTP is widely regarded as the cellular-molecular mechanism of learning and memory in the hippocampus. Usually, the findings obtained in electrophysiological studies confirm the results of behavioral assessments (17-20). Evaluations of the molecular mechanisms of learning and memory have demonstrated the existence of both positive and negative regulators of synaptic plasticity and memory formation (6, 17). Positive regulators such as calcium/calmodulin-dependent protein kinases, mitogen-activated protein kinase, and protein kinase A (PKA) are critical for initiating synaptic plasticity and

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memory (17, 21). However, some phosphatases such as calcineurin and calcium/calmodulin-dependent protein kinase and protein phosphatase 1 are known as negative regulators and inhibit neuroplasticity and memory (22). Studies have shown that calcineurin as a negative regulator is widely present in various areas of the hippocampus and its activity leads to dephosphorylation of some intracellular proteins that ultimately affect the induction of LTP and memory (23, 24). In support of these findings, Malleret et al. surveyed the impact of genetically inhibiting of CaN on learning, memory, and synaptic plasticity. According to the results of their study, inhibition of endogenous CaN enhances LTP in the hippocampus in vitro and in vivo. Additionally, they indicated that CaN can act as an inhibitory constraint on PKA-dependent pathways and downregulate signals that support memory function and synaptic plasticity (8).

Considering the negative effects of CaN on synaptic plasticity, administration of TAC as a CaN inhibitor may lead to the improvement of synaptic plasticity in the hippocampus. Some previous studies investigated this hypothesis and reported that administration of TAC increased the intrasynaptosomal calcium concentration and induced the calcium-dependent release of glutamate neurotransmitter from synaptosomes of the brain and improved spontaneously firing neurons (25, 26). Besides, according to some reports on the contribution of glutamate to synaptic plasticity (27), it seems that increased glutamate level through inhibition of CaN may be responsible for enhanced synaptic plasticity and LTP induction by TAC.

A study by Moradpour et al. added further evidence for the relationship between TAC and neuroplasticity. Their results revealed that dose-dependent administration of TAC increased the magnitude of field excitatory postsynaptic potential (fEPSP) in the hippocampus slices. However, they reported that TAC had no significant effects on the magnitude of PS (Population Spikes) (28). The discrepancy between the effect of TAC on fEPSP slope and PS amplitude indicated that TAC could have different effects on the induction of fEPSP and PS, which is evaluated by E-S coupling curves. A previous study evaluated this hypothesis and reported that microinjection of TAC strengthened the effect of HFS (High Frequency Stimulation) on E-S coupling curve (28). According to some studies, CaN regulates the activities of different ion channels through the dephosphorylation of different target proteins (29). Therefore, the administration of TAC affects the performance of ion channels. As duBell et al. reported, TAC led to prolonged duration of the action potential of ventricular myocytes, which resulted from the change of ion channels action (30). Moreover, in a study conducted by Terashima et al. reported that TAC could regulate the actions of K^+ channels. For instance, TAC was found to increase the open time of the Ca^{2+} activated K^+ channel in hippocampal neurons (31).

Evidence from different studies suggests that the hippocampus is highly susceptible to the neurodegenerative impacts of transient global cerebral ischemia (TGCI) (32-35). On the other hand, TAC decreases neuronal death and damage in the hippocampus after TGCI (36, 37). These findings indicate that TAC might be effective in the treatment of ischemia-induced hippocampal neuronal death. Lee et al. investigated the effects of TAC on the induction of LTP in the culture of hippocampal slice. According to their results, TAC promotes the survival of neural cells in the hippocampus during kainic acid-induced excitotoxic injury. Therefore, they suggested that the survival of neural cells and recovery of their activity due to the neuroprotective impacts of TAC may lead to an increase in the synaptic strength and affect the functional synaptic activity (38).

Previous evidence also demonstrated that the activation of CaN has been involved in the alterations of dendritic spine morphology (39). Spires-Jones et al. investigated the effects of CaN inhibition using TAC treatment on neuronal morphology. Their results showed that treatment with TAC could lead to significant growth in basal dendritic spine density and a rise in the complexity of basal dendritic trees of neurons (40). Thus, these structural alterations in dendrites may underlie both the enhanced synaptic plasticity and memory performances.

Some morphological modifications including synapse and dendritic spines loss in neurons occur in the Alzheimer's disease, which can contribute to neuroplasticity dysfunction (41, 42). According to Wu et al., CaN mediates Aβ-induced morphological modifications, including spine loss in cultured neurons, and the elimination of CaN in Alzheimer's disease can abolish plaque-associated pathologic modifications in dendrites and dendritic spines (43). Besides, as reported by Rozkalne et al., administration of TAC leads to an amelioration of dendritic spine loss in plaque-bearing transgenic mice (44). This finding suggests that TAC administration may be a

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neuroprotective agent for amyloid beta-induced synaptic modifications through CaN inhibition. Overall, it could be concluded that TAC administration contributes significantly to the electrophysiological responses, including the activity of ion channels, LTP induction, and synaptic plasticity.

Effects of TAC on learning and memory: Learning and memory are the ability for acquisition, maintenance and retrieval of information which are classified in different ways. Complex mechanisms play a role in learning and memory, ultimately leading to biochemical, morphological and physiological changes at the level of synaptic and neural networks. Learning and memory cannot be fully understood independently of each other since they are highly interrelated (45). As mentioned previously, there is a relationship between CaN and cognitive functions such as learning and memory. A large number of studies indicate that CaN, as a calcium/calmodulin-dependent phosphatase, has an inhibitory impact on learning and memory functions (6).

Spatial learning and memory are the ability to encode, store, and retrieve information about specific environmental situations relative to each other and to individuals. Malleret et al. investigated the impact of CaN on spatial learning and memory. They reported that memory for spatial location of object is enhanced by the genetic inhibition of CaN at short retention intervals (8). In order to survive, animals develop fear reactions to unsafe situations. The neural mechanism of learned fear has survival importance for animals, since they must estimate danger from seemingly neutral contexts (46). The hippocampus and amygdala are the main structures involved in fear learning and memory (47).

A previous study investigated the effect of CaN on fear learning and memory and reported that reduced CaN action could improve fear learning and memory (22). These findings propose that the restriction of CaN action can affect different types of learning and memory. Considering the inhibitory effect of CaN on different types of learning and memory, the administration of TAC can probably improve learning and memory function. In support of this idea, some studies showed that administration of TAC increased the concentration of intrasynaptosomal calcium and facilitated the calcium-dependent release of glutamate from brain synaptosomes (25, 26). On the other hand, some studies have also shown that glutamate is one of the most important excitatory neurotransmitters in the mammalian CNS and the principal neurotransmitter employed by pyramidal cells in the cerebral cortex and numerous hippocampal tracts (27). Therefore, given the contribution of glutamate to cognitive functions such as learning and memory, it appears that increased glutamate levels due to the administration of TAC may be responsible for the improvement of TAC-induced cognitive functions.

It has been proved that the processes of learning and memory are usually conceptualized as containing three steps: encoding, storage, and recall. Encoding is explained as the initial registration and acquisition of information. Step of storage is the maintenance of information over time in the CNS, while recall is the process in which the saved information is brought back into conscious awareness and affects ongoing behavior (45). It is well established that TAC selectively affects acquisition and recall of learning and memory processing in CNS (8).

In support of this finding, in a recent study, Moradpour et al. investigated the effect of TAC on recall of passive avoidance memory. According to their results, through inhibition of CaN, TAC leads to improved retrieval of passive avoidance memory in a dose dependent manner (28). Besides, according to some pervious studies, there is a relationship between inhibition of CaN and olfactory memory (48). In line with these findings, Christie-Fougere et al. reported that TAC as a CaN inhibitor prolonged the period of CREB phosphorylation in mitral and granule cells of dorsomedial and dorsolateral quadrants of the olfactory bulb and strengthened the odor preference memory (49).

TAC has long-lasting protective effect against neuropathological modifications. Tanaka et al. reported that administration of TAC improved the learning deficits. According to the results of their study, TAC recovers the learning deficits mostly because of preventing neuropathological modifications (50). Another study reported that the intermediate and long-term recognition memory impairments in Tg2576 mice were abolished with the administration of TAC as a CaN inhibitor (51).

Therefore, it can be concluded that CaN is negatively associated with learning and memory functions, and TAC administration improves different types of learning and memory functions. Overall, these findings indicate that TAC exerts at least some of its effects on numerous cognitive functions such as learning, memory, and neuroplasticity by inducing the inhibition of the negative effects of CaN on cognitive functions and also changes in glutamate level (Fig. 2).

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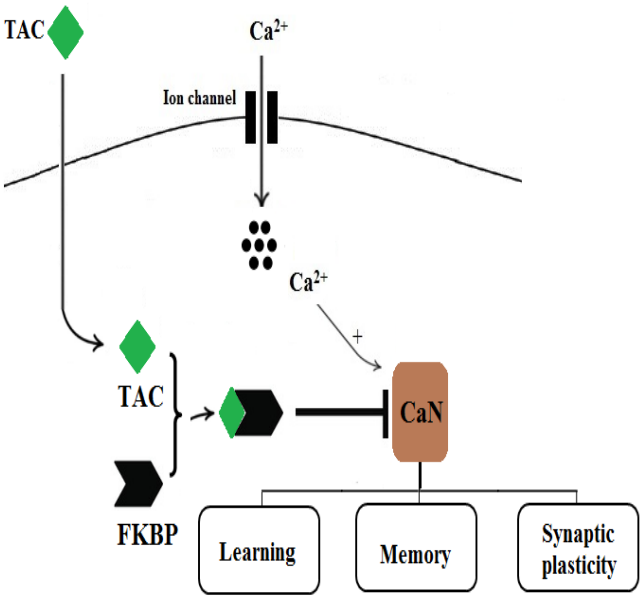

Figure 2. Inhibitory effect of TAC on CaN activity. **TAC exerts its inhibitory effect of CaN following binding to the protein domain of FKBP. Then, CaN inhibition by TAC leads to the alternation of cognitive functions such as learning, memory, and synaptic plasticity.**

Effects of TAC on Free radicals: Free radicals are chemical structures that have unpaired electrons in their external orbit. This property leads to a highly reactive state and a propensity for reactions. The imbalance between the production of prooxidants and antioxidant systems within a cellular system leads to oxidative stress (52, 53). A great number of studies confirmed the involvement of free radicals in damage of macromolecules of the cell containing fatty acid, DNA, and protein (54, 55). On the one hand, the brain is highly vulnerable to oxidative stress due to its high oxygen turnover, which leads to the formation of oxygen-related free radicals. Moreover, brain has high levels of polyunsaturated fatty acids and low antioxidant activity when compared to other organs and tissues (56). Therefore, accumulation of free radicals is very hazardous in the CNS.

Much evidence demonstrates that oxidative stress caused by accumulation of free radicals is involved in memory impairment and synaptic dysfunction because the production of free radicals has been related to neuronal death and decay cognitive functions, while administration of antioxidants can abolish these deficits (57-59). In line with these results, Fukui et al. reported that oxidative stress significantly impaired spatial learning and memory in the radial-arm water maze. Furthermore, they reported that these effects can partially attenuate by administration of antioxidant compounds (60). Previous evidence demonstrated that TAC has beneficial and protective effects against functional disorders caused by oxidative stress. It has been established that TAC is able to prevent DNA fragmentation (61-63).

One of the most important effects of free radicals is lipid peroxidation, which leads to the disturbance of cell membranes (64). Kaymaz et al. investigated the effect of TAC on lipid peroxidation in injured spinal cord tissue. According to the results of their study, administration of TAC decreases lipid peroxidation (65). It has been well established that malondialdehyde (MDA) is end product of lipid peroxidation and is commonly measured to be an excellent index of lipid peroxidation (64, 66). A previous study demonstrated that TAC decreases the parameters of oxidative stress, including the level of MDA and the activity of myeloperoxidase (67).

Inhibition of dephosphorylation of nitric oxide synthase decreases the generation of nitric oxide and NO-dependent free radicals that cause damage in different cells (68, 69). Moreover, CaN regulates nitric oxide synthase activity in a calcium-dependent manner (70). Phosphorylated NOS is inactive, and dephosphorylation of NOS by CaN leads to the formation of NO that can then react with superoxide radicals to generate peroxynitrite radicals (68, 70). Peroxynitrite is a highly reactive radical that leads to cytotoxicity, neurodegeneration, neuronal cell death and apoptosis (71). TAC leads to cerebroprotective activities by inhibition of NO formation, indirectly avoiding the CaN-mediated dephosphorylation of NOS (68). On the other hand, a previous study has been reported that TAC can decrease the generation of superoxide radical (72).

According to these findings, it can be concluded that CaN causes the formation of NO that can then react with superoxide radicals to generate peroxynitrite radicals, while TAC decreases the level of superoxide radicals and inhibits the formation of NO (Fig. 3). Therefore, neuroplasticity dysfunction and cognitive impairment are associated with the accumulation of oxidative damage to macromolecules, and these negative effects can be nullified by TAC.

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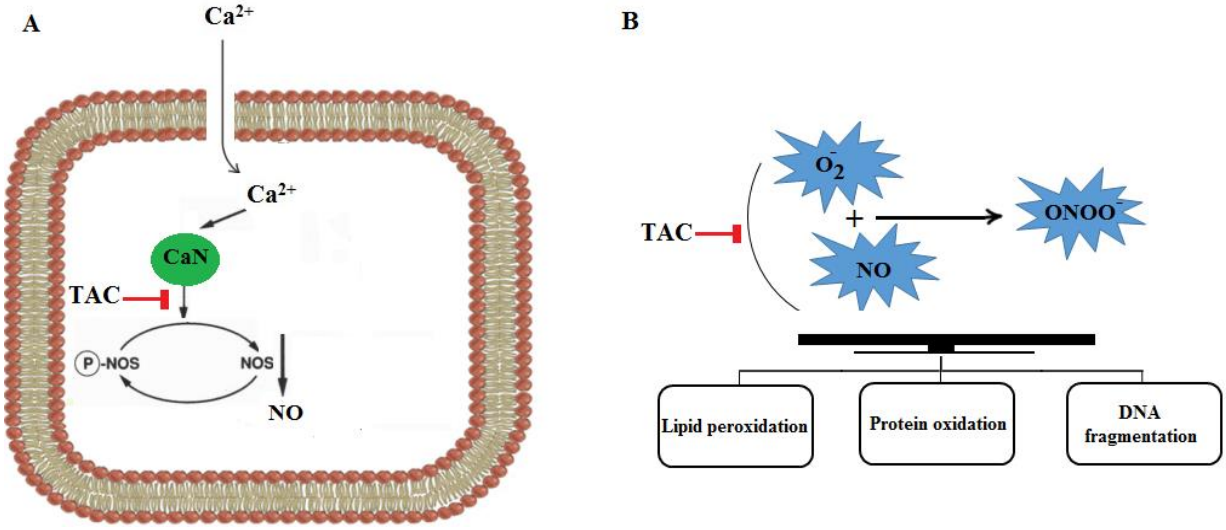

Figure 3. Inhibitory effect of TAC on the generation of free radicals. **CaN leads to the formation of NO, which can then react with superoxide radicals to generate highly reactive peroxynitrite radicals. Therefore, CaN increases the level of free radicals and then leads to lipid peroxidation, protein oxidation, and DNA fragmentation, while TAC through the inhibition of CaN decreases the level of superoxide radicals and inhibits the formation of NO.**

Discussion

The results obtained from experiments agree with the fact that TAC can cause several central effects. Synaptic plasticity, learning, and memory are the most complex functions of the CNS for information management. Based on the findings of this article, TAC improves cognitive functions such as learning, memory, and synaptic plasticity, described in detail in the present article. Besides, this review article argued on the diverse mechanisms for the neuroprotective effects of TAC on cognitive functions. Regarding the inhibitory effects of CaN on hippocampal-based learning, memory, and synaptic plasticity, it seems that some of these effects on the functions of the neuronal system caused by tacrolimus may be due to inhibition of CaN activity.

It has been well established that synaptic plasticity is commonly regulated by the release of several neurotransmitters from the presynaptic neurons. Glutamate is one of the most important excitatory neurotransmitters in the CNS that plays a critical role in memory functions, synaptic plasticity and LTP induction. The inhibition of CaN is also associated with the increasing of the glutamate concentration, which may be considered as another potential mechanism for improvement of learning, memory and synaptic plasticity induced by TAC. Increasing evidence indicates that oxidative stress can lead to synaptic plasticity dysfunction and memory impairments. Brain is especially vulnerable to oxidative stress, because it uses a large level of oxygen, has plentiful lipid content, and has low antioxidant activity. On the other hand, the administration of TAC decreases the level of superoxide radicals and inhibits the formation of NO and NO-dependent free radicals that cause damage in different cells. Thus, the protective effect of TAC against oxidative stress suggests that another possible pathway for the effects of TAC on neuroplasticity and memory functions is through the decrease in the level of free radicals. Based on the current review, it is suggested that TAC as a CaN inhibitor affects cognitive functions of the CNS through different pathways. However, further investigations are needed for understanding the efficacy of TAC on the cognitive functions.

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