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REVIEW ARTICLE

Investigation of transcription factor cyclic AMP response element-binding protein activator in rodent model of intracerebral hemorrhage

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ABSTRACT Neurological disorders are a heterogeneous group of diseases of the nervous system having different etiologies. Intracerebral hemorrhage (ICH) having a common final finding, i.e., cognitive and motor impairment, and this may occur as a result of multineurotransmitter deficits, decreased availability of intracellular molecules, and axonal transporters through which the different neurons communicate with each other to maintain neuronal excitation and cognitive functioning. Secondary messengers such as cyclic nucleotides, cAMP and cGMP, play a critical role in neuronal signaling and synaptic plasticity by activation of several pathways such as cAMP/protein kinase/cAMP response element-binding protein (CREB) and cGMP/protein kinase G (PKG)/CREB and factors such as brain-derived neurotrophic factor, semaphorins, netrin-1 and 16, nerve growth factor, and neurotrophin 3,4,5-inhibitory factors associated with myelin and myelin-associated glycoprotein. These pathways and factors are well known to help neuronal survival, help neurogenesis, and protect neurons from injury. Thus, enhancement and prolongation of cAMP and cGMP signaling can be helpful in dealing with neurodegenerative disorders including ICH. Forskolin (FSK), a major diterpenoid isolated from the roots of Coleus forskohlii, directly activates the enzyme adenyl cyclase, thereby increasing the intracellular level of cAMP and leading to various physiological effects. Based on the important and versatile role of cAMP signaling in regulation of neuronal functions, the focus of the research was directed to investigate the role of direct adenyl cyclase activator FSK, cAMP selective enhancement in experimental models of ICH.

KEYWORDS
cerebral hemorrhage,
neuroinflammation,
cyclic AMP,
Forskolin

INTRODUCTION

Cerebral hemorrhage

Neurological disorders are a heterogeneous group of diseases of the nervous system having different etiologies. They represent illnesses of the selective regions of the brain and nervous tissues that control vital physiological functions such as learning and memory, posture, and coordination of movements of nerves/muscles.[1] Central nervous system disorders including Alzheimer's disease (AD), Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, brain abscess, multiple sclerosis, spinal cord injury, cerebral stroke, and traumatic brain injury are characterized primarily by neurodegeneration and neuroinflammation.[2]

Intracerebral hemorrhage (ICH) is characterized by oxidative stress, excitotoxicity, neurotransmitter deficits, mitochondrial energy failure, and neuronal cell death, which leads to behavioral and motor dysfunctions.[3–6] Stroke is an acute cerebrovascular disease, which occurs as a result of sudden interruption of blood supply[7] to a part of

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brain typically by a thrombus or embolus occlusion or hemorrhage due to rupture of blood vessels[8] and age-related,[6] progressive, irreversible,[5] chronic neurodegenerative disorder.[9,10]

Patients who have had a stroke are at an increased risk of neurodegenerative complications compared to the people of the same age group, and the risk is posing major health challenge in India because of its high prevalence rate.[11,12] Stroke that results from acute insult to the brain[13,14] remains the third most common cause of death in industrialized nations and is at the seventh position among the 10 leading causes of death in the developed countries.[15] It is estimated that by 2050, the number of patients with cerebral stroke could be as high as 25 million.[16,17]

ICH having a common final finding, i.e., cognitive and motor impairment, which may occur as a result of multineurotransmitter deficits,[18] decreased availability of intracellular molecules and axonal transporters[19] through which the different neurons communicate with each other to maintain neuronal excitation and cognitive functioning.[19] At cellular levels, the storage of short- and long-term memory is associated with gene expression, *de novo* protein synthesis, and formation of new synaptic connections.[20]

Adenylyl cyclase (AC)/cAMP/protein kinase (PKA) pathway and brain

Intracellular molecules also known as secondary messengers such as cyclic nucleotides, i.e., cAMP and cGMP, play a critical role in neuronal signaling and synaptic plasticity by activation of several pathways such as cAMP/PKA/cAMP response element-binding protein (CREB) and cGMP/protein kinase G (PKG)/CREB and factors such as brain-derived neurotrophic factor (BDNF),[21] semaphorins,[22] netrin-1 and 16,[23] nerve growth factor,[24] and neurotrophin 3,4,5-inhibitory factors associated with myelin and myelin-associated glycoprotein.[25,26] These pathways and factors are well known to help neuronal survival, to help neurogenesis, and to protect neurons from injury.[27,28]

Elevation of cAMP causes both short- and long-term increase in synaptic strength[29–31] and stimulates cholinergic neuronal cells to release acetylcholine.[32] But the levels of cAMP and cGMP are reported to be decreased in neuropathological conditions including cerebral stroke and AD.[33–35]

It has been reported that cerebral ischemia-induced energy failure also leads to reduction in the levels of key signaling molecules such as cAMP and cGMP and results in disruption of cAMP/PKA/CREB[33] and cGMP/PKG/CREB signaling pathways.[36] On the other hand, it has also been reported that cerebral ischemia-induced energy failure leads to impair hippocampal long-term potentiation (LTP), a neurophysiological correlate of memory,[37] by inhibiting the activation of both cAMP/PKA/CREB[34] and cGMP/PKG/CREB pathways in ICH pathology.[35] The pyramidal CA1 neurons of hippocampus, involved in learning and memory become vulnerable target in cerebral stroke.[38] Further, cAMP or cGMP dependent CREB phosphorylation has too been reported to induce long-term memory (LTP)[39] and inhibit apoptotic and necrotic cell death.[40]

CREB activation and brain

CREB is a transcriptional factor responsible for the synthesis of proteins that are important for the growth and development of synaptic connections and that increase the synaptic strength.[41] Thus, agents that enhance the cAMP/PKA/CREB and cGMP/PKG/CREB pathways have potential for the treatment of stroke, AD, and other neurological diseases.[42] cAMP and cGMP mediate signaling of several neurotransmitters including serotonin, acetylcholine, glutamate, and dopamine, which play important roles in cognitive functioning.[43,44]

The activation of the cAMP-dependent PKA significantly inhibits tumor necrosis factor-α[45,46] and inducible nitric oxide synthase in astrocytes and macrophages,[47] which are implicated in neuroinflammation[45] and oxidative stress, respectively.[48]

cAMP system is closely involved in the regulation of BDNF expression too,[49–51] which play an important role in neuronal survival,[21] synaptic plasticity,[52] learning, and memory.[50,51] Further elevation of cAMP and cGMP levels restores the energy levels,[53] reduces excitotoxic damage,[54] prevents Aβ-mediated neurotoxicity,[34,35] enhances biosynthesis and release of neurotransmitters,[44,55,56] and inhibits apoptotic and necrotic cell death,[57] leading to improvement in cognitive functioning[58] (Figure 1).

Central administration of cAMP and cGMP has been reported to enhance neuronal survival[59] and memory performance.[58,60] In view of the above results, the enhancement and prolongation of cAMP and cGMP signaling can thus be helpful in dealing with neurodegenerative disorders including ICH. This can be accomplished by activating the adenyl cyclase enzyme, which metabolizes these cyclic nucleotides. Forskolin (FSK), a major diterpenoid isolated from the roots of Coleus forskohlii, directly activates adenyl cyclase, thereby increasing the intracellular level of cAMP and leading to various physiological effects.

Despite substantial research in neuroprotection, treatment options are still limited to supportive care and the management of complications. Currently, available drugs provide symptomatic relief but do not stop progression of disease.[11] Thus, the development of new therapeutic strategies remains an unmet medical need. The failure of current drug therapy may be due to their action at only one of the many neurotransmitters involved[61] or their inability to upregulate signaling messengers reported to have an important role in neuronal excitability,[62] neurotransmitter biosynthesis and release,[63] neuronal growth and differentiation,[57] synaptic plasticity, and cognitive functioning.[64]

Future perspectives and treatment approach

Phytochemicals drugs have been used since ancient times as medicines for treatment of a range of diseases. Medicinal plants have played a key role in world health. In spite of the great advances observed in modern medicine in recent decades, plants still make an important contribution to health care. Medicinal plants are distributed worldwide, but they are most abundant in tropical countries. Over the past decade, interest in drugs derived from higher plants, especially the phytotherapeutic ones, has increased expressively. It is estimated that about 25% of all modern medicines are directly or indirectly derived from higher plants. Phytomedicines are standardized herbal preparation consisting of complex mixtures of one or more plants, which are used in most countries for the management of various diseases. Other characteristics of phytochemicals are their wide therapeutic use and great acceptance by the population. In contrast to modern medicines, phytochemicals are frequently used to treat chronic diseases. Phytochemicals are normally marketed as standardized preparations in the form of liquid, solid, or various preparations. Compared with well-defined synthetic drugs, phytochemicals exhibit some following marked differences:

- The empirical use in folk medicine is a very important characteristic.
- They have a wide range of therapeutic use and are suitable for chronic treatments.
- The occurrence of undesirable side effects seems to be less frequent with herbal medicines, but well-controlled randomized clinical trials have revealed that they also exist.
- They usually cost less than synthetic drugs.

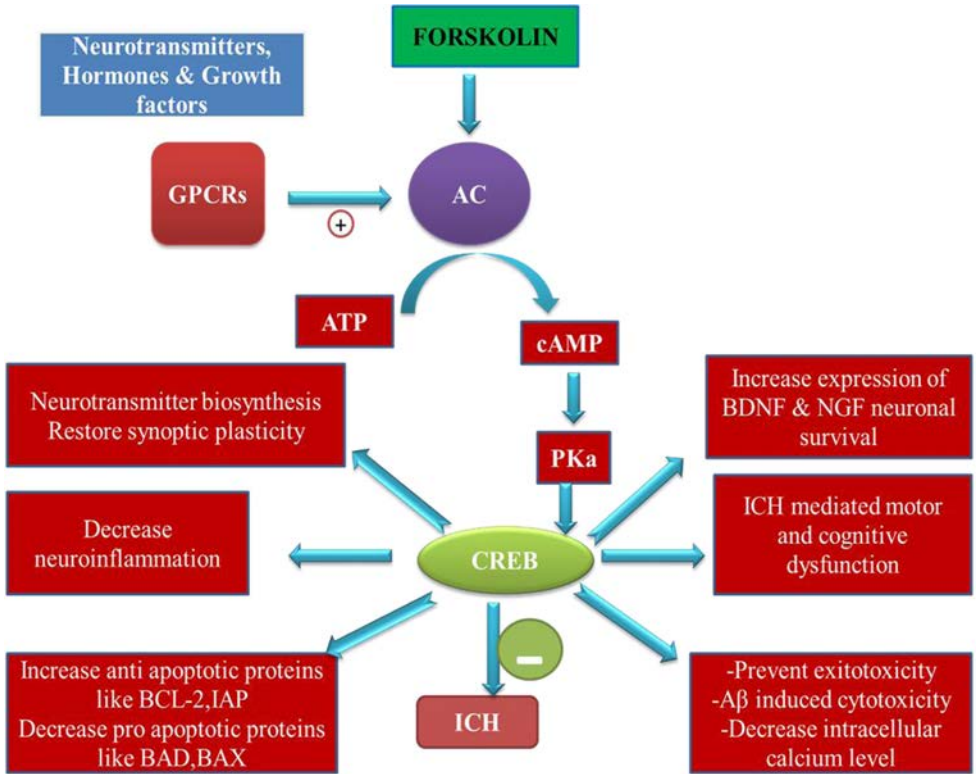

Figure 1 Neuroprotective action of Forskolin-mediated AC/cAMP/PKA/CREB activation. BDNF, brain-derived neurotrophic factor; ICH, intracerebral hemorrhage; NGF, nerve growth factor; PKA, protein kinase; AC, adenylyl cyclase; BAD, Bcl-2-associated death promoter; BAX, Bcl-2-associated X protein; BCL-2, B-cell lymphoma 2; GPCR, G protein-coupled receptor; CREB, cAMP response element-binding protein; IAP, inhibitor of apoptosis protein.

CONCLUSION

Therefore, as already mentioned above, one of the alternatives to enhance the levels of cAMP and cGMP secondary messengers or to enhance CREB phosphorylation can be achieved through activation of adenyl cyclase by herbal phytochemical FSK, which are meant to increase these cyclic nucleotides. Based on the important and versatile role of cAMP signaling in regulation of neuronal functions, the focus of the present research was directed to investigate the role of direct adenyl cyclase activator FSK, cAMP selective enhancement in experimental models of ICH.

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