Repercussion of cAMP and EPAC in Memory and Signaling

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ABSTRACT

It is well recognized that cyclic adenosine monophosphate (cAMP) signaling within neurons plays a key role in the foundation of long-term memories. Memory storage is the process that demands the movement of signals, neural plasticity, and the molecules which can transfer the signals from the sensory neuron to the dorsal root ganglion (DRG) neurons and later into the temporal region of the brain. The discovery of cAMP in 1958 as the second messenger also had a role in memory formation and other neural aspects. Further, in 1998 the scientists found that cAMP does not just activate protein kinase A (PKA) but also exchange protein directly activated by cAMP (Epac) which has an active role to play in hyperalgesia, memory, and signaling. The cAMP has three targets, hyperpolarization-activated cyclic nucleotide modulated (HCN) channels, protein kinase A (PKA), and exchange protein activated by cAMP (Epac). Different research has exposed that both PKA and HCN channels are significant for long-term memory creation. Epac is a cAMP-dependent guanine nucleotide exchange factor for the small G proteins including Rap1. However, slight information is there about the role of Epac in this process. The effects of cAMP are predominantly imparted by activating protein kinase A (PKA) and the more newly discovered exchange proteins are directly activated by cAMP 1 and 2 (EPAC1 and EPAC2). This review provides an insight regarding the function and role of both of these secondary messengers in memory and nerve signaling.

ABBREVIATIONS

cAMP	Cyclic adenosine monophosphate
EPAC	Exchange protein directly activated by cAMP
DRG	dorsal root ganglion
PKA	Protein kinase A
PGE2	Prostaglandin E_2
PKC	protein kinase C
PSD-95	Postsynaptic density protein 95
Rap-1b	Ras-related protein
ERK1/2	extracellular signal-regulated kinase
PKB	Protein kinase B
Rap-PLC-ε-ERK	Ras-related protein- Phospholipase-ε extracellular-signal-regulated kinase
Rac	Ras-related C3 botulinum toxin substrate
miR	MicroRNA
Zif268	Zinc finger-containing transcription factor 268
P38 MAPK	p38 mitogen-activated protein kinases
GTPases	guanosine triphosphate
CNB	Cyclic nucleotide binding
DEP	Dishevelled-Egl-10-Pleckstrin
REM	Ras exchange motif
GTP	guanosine triphosphate
GDP	guanosine diphosphate

PLCs	Phospholipase Cs
MAPKs	mitogen-activated protein kinases
IB4 +	isolectin B4 positive
CMIQ	4-cyano-3-methylisoquinoline
8-pCPT-2-O-Me-cAMP	8-[(4-chlorophenyl)thio]-2'-O-methyl-adenosine cyclic 3',5'-cyclic monophosphate
PI	phosphatidylinositol
PLD	phospholipase D
CPT	8-(4-Chlorophenylthio)adenosine
εV1–2	EAVSLKPT-acid
PI-PLC	Phosphatidylinositol-specific phospholipase C
ERK	extracellular-signal-regulated kinase
P2X3	purinergic receptor
P2X	Purinergic receptors
ATP	Adenosine triphosphate
α, β-meATP	α, β-methylene ATP
CFA	Complete Freund's Adjuvant
Sp-6-Phe-cAMPS	N6- Phenyladenosine- 3', 5'- cyclic monophosphorothioate, Sp- isomer
Sp-8-pCPT-2'-O-Me-cAMPS	8- (4- Chlorophenylthio)- 2'- O- methyl-adenosine- 3', 5'- cyclic monophosphorothioate, Sp- isomer
DILI	Drug-induced liver injury

Introduction

Memory impairment is a single term that includes all the complications related to signaling, recall, and retrieval of the stored information. This difficulty in cognition of the daily basic needs of a person is generally considered to be because of the brain. The brain is divided into sections that perform the actions according to the desire [1]. The work by Milner et al. suggested that the memory disorder such as amnesia is localized to the limbic system containing hippocampus, medial temporal lobe, and thalamus [2]. Further Larry Squire classified memory into explicit or declarative memory and implicit or procedural memory. In 1992, squire defined explicit memory as the one which needs the subjects to concentrate on the prior information or facts. Whereas in the implicit memory the access to the information is unintentional or the actions are involuntary this can be explained with the simple retrieval actions against any sensory input [3].

The involvement of neuron synapses was not in the picture until the 1960s. A concept of memories in the form of a bioelectric field within the neurons was explained by Karl Lashley and Ross Addeys. This further led to Ramon y Cajal's idea which said that memory and learning are due to the changes in the strength of the synapses [4]. Konorski's idea added the information on the models of learning by Hebb (1949). Later Spencer and Kandel in literature focused on the behavioral changes that occur in the neuronal components during the learning and memory storage behaviors [3].

The explicit memory functioning was getting cleared by then and now it was the time to focus on the implicit memory and their functioning. While exploration towards the implicit memory initiated the basic difference with that of the explicit memory. Implicit memory is the one that is based on experiences and does not require any interfere of the consciousness. The first reference to the implicit memory was in the year 1649 by Descartes. The observation revealed that the daunting or aloof experience in childhood may continue to show the signs until the end of his life [5, 6].

After differentiating the memory into 2 categories the next step was to analyze the behavior of the implicit memory. The work towards this started in the year 1964 and many models were studied. The observations of the eye blink of the rabbits in the response, relaxing reflex of the cats and dogs, and the invertebrate reflex such as the one with that of the Aplysia and Tritonia. The complete study was aimed to find the neural circuit which acts as the mediator for the changes in the reflex and behavior, it also helped to understand the synaptic sites which actively participated in the memory functioning and learning during these stages. These works also focused on the changes in the cellular levels during the storage of these memories [5–10].

To understand the behavior of learning and memory a group of scientists led by Randolf Menzel observed the pattern followed by bees to get the nectar from the flower. The set of bees sucked the nectar from the colored or odor flower. This was proved by Karl von Frisch in his experiment in the year 1910 [11]. Similarly studying the reflex behavior response of Hermissenda on the stimulation by the visual and rotational stimuli had two effects activation or arousal and attraction [5]. The actions of the ganglion of Aplysia towards the tactile stimulation by siphon and mantle shelf revealed the set of responses. These responses were interneural studied by I. Kupferman and E. R Kandel. The first set of responses was defensive withdrawal symptoms and the second response was spontaneous with drawl symptoms [8]. This led to the need for an in-depth study of the memory and the function of the neurons responsible to show the set of actions.

The need to study the mechanism of memory was on the rise. The primary finding of the memory was on the short-term memory. Any of the actions by an invertebrate such as the color and odor identification by bees or the gill movement of Aplysia was due to the changes in the synaptic cleft of the neurons. This led to the study of the role of neurotransmitters in short-term memory [3]. The different neural function of Epac and its mechanism has been illustrated in ▶ **Table 1**. This review provides an insight regarding the role of Epac protein and cAMP on neurophysiological function, especially on memory and learning.

Molecular Biology of Memory

Role of smaller molecules in the plasticity of neuron

Neural or brain plasticity is the ability of the brain to respond or change its action as per the requirement of the intrinsic or extrinsic stimuli. To deliver required actions, the brain often must rearrange itself in its function or connections [11]. The mechanism of memory storage or encode is probably because of the change in the strength of the connections [12]. The work by Brunelli et al. in

▶ **Table 1** Different neural function of Epac and its mechanism.

S. No.	Functions by Epac	Action through
1.	Axon Remodelling	Neuroligin-3, PSD-95, Rap1B
2.	Axon Regeneration	Spinal cord
3.	Outgrowth or differentiation	ERK1/2, PKB/Akt
4.	Anxiety and depression	Rap-PLC-ε-ERK
5.	Autism or schizophrenia	Rap
6.	Alzheimer's or dementia	Rap1, Rac, PKB/Akt
7.	Huntington's disease	Rap2B, Ca2+, calpain
8.	Learning and memory	miR-124 suppression and Zif268 translation
9.	Pain perception	Rap1-PLC-ε-ERK
10.	Neurotransmitter release	P38 MAPK

▶ **Table 2** Types of secondary messenger with their functions.

S. No	Types of messenger	Example	Functions
1	Cyclic nucleotide	cAMP	Transmits signals within cytosol
2	Lipid messenger	Phospholipase	Transmits signal within cell membrane
3	Ionic messenger	Ions such as sodium, calcium	Transmits signal within and between cellular compartment
4	Gases and free radicals	Nitric oxide	Transmits signal throughout and even to the neighboring cell

1976 revealed the action of three neurotransmitters to produce the motor action on the sensitivity towards the gill withdrawal reflex of *Aplysia*. The outcome of this research was, even without protein, the transmission of signals between the neuron was possible. The smaller molecule's action was hence into the lights. The results of the study also show the release of three major neurotransmitters on the stimulus to *Aplysia* were the dopamine, serotonin, and octopamine. Of all the neurotransmitters the serotonin had the major role to play [12–14]. The serotonin was responsible for the increased output of cAMP at the synapses due to the external sensitizing stimuli.

Secondary messenger

In a single term, these structures can be easily understood by the transporter. The function of the secondary messenger is to carry the inputs from the receptor surface to the reacting proteins. The activation of the secondary messenger after stimulation is received by a receptor cell. Many secondary messengers in the resting time of the cell are low and it actively increases with the receptor signal [15]. Different types of secondary messenger with their functions have been mentioned in ▶ **Table 2**.

Role of cAMP in Neural Signaling

cAMP (Cyclic Adenosine Monophosphate or Adenosine 3′,5′-cyclic monophosphate) was a silent effective secondary messenger until 1958. Earl Sutherland came up with the discovery of cAMP as a second messenger [3]. cAMP and other such molecules are named as the second messenger because of their function as the transporter between the original neurotransmitter or hormone and the final cell response of intermediate metabolism. The cyclic adenosine monophosphate is produced by the action of the adenyl cyclase enzyme on ATP [16]. The cAMP was always produced in the body, to test the functioning of the second messenger the Brunelli et al. experimented by injecting the cAMP. The result of injecting the cAMP to the sensory neuron was the increased neurotransmitter release in the synaptic spaces between the sensory and motor neuron. This study on gill withdrawal reflux increased the understanding on cAMP [3].

The initial study on the involvement of cAMP towards long-term memory by different scientists indicated the requirement of PKA. PKA is sensitive and activated by cAMP and carries out memory storage functioning. The process by which activated PKA carries out memory formation was found to be phosphorylation of kinases and the transcription. But the work carried out by the Nan Ma et al. indicated the direct cAMP involvement in the formation of memory by Epac which is an exchange protein activated by cAMP [17]. The previous studies already indicate the ability of Epac in improving the synaptic potentials of the hippocampus [18].

The experimentation by Nan Ma et al., in which mice were understudy for 2–4 months, to understand the importance and need of Epac in the hippocampal strength and its pharmacological presence [17] and the study carried out by Jennifer et al. on mouse also revealed that the Epac acts on the hippocampus and its synapse to form long term memory [18].

It was in 1983 when Hawkins and his team were successfully able to understand and explain the different conditions involved in the gill-withdrawal reflex. They also explained the cellular analysis of the reflexes in the gill movement. The experimentation of the stimulation of the siphon and the shock to the tail revealed that the withdrawal reflexes were increased when both the sensation was given to the *Aplysia*. Whereas when the sensation was only because of the stimulation of the siphon or due to the shock to the tail the reflexes were reduced. From the experimentation, it was also noted that the coupled or dual training produced the increased neurotransmitter firing from the sensory to the motor neuron. this also formed a great synaptic transmission forming a monosynaptic connection. The experimentation by a different procedure, that is the stimulation to two different sites siphon and the mantle shelf, revealed the stimulation to the siphon was enhanced. There were further experiments that had the conclusion of the presynaptic facilitation as the reason for the increased transmitter release. Later the experiments carried out by Tom Abrams had the evidence with the calcium playing its role in the activation and in the improved functioning of the adenyl cyclase which was responsible for the production of cAMP. The conclusive pieces of evidence were found to believe that the serotonin presence increased the production of cAMP by adenyl cyclase. It also revealed the reason for the enhanced activity of the cAMP. The calcium present in the cell increases the production of cAMP and it increased the neurotransmitter [3].

Understanding the Epac

Epac (exchange protein directly activated by cAMP) or cAMP-GEF (cAMP-regulated guanine exchange factor), have been an important protein playing part in neuro signalling. These proteins comprise a CBD that is similar to that of the prokaryotic transcription regulator, PKA R subunits and, cAMP receptor protein (CRP). With high affinity, Epac proteins bind to cAMP and activate the Ras superfamily small GTPases Rap1 and Rap2. Rap1 was at first acknowledged as an antagonist for the transforming function of Ras. Rap1 can be stimulated in response to a variety of second messengers together with cAMP. Although PKA can phosphorylate Rap1 at its C-terminus, PKA phosphorylation is not needed for the cAMP-dependent activation of Rap1 [19].

cAMP is a well-known molecular structure and its function of the activation of certain types of ion channels in the plasma membrane. The activation of PKA by cAMP to produce various effects in the cell was familiar but a new term Epac also joined the list of active agents in the nervous system. It is a sensory protein with the function to bind cAMP and activate the GTPases. It was discovered in the year 1998, by de Rooij et al. while the search for the mechanism of cAMP-linked GTPase activation was an understudy. The database screen search for the mechanism of activation of Rap1 came up with the visualization of the striatum by Kawasaki et al. revealing the presence of proteins bound to the cyclic nucleotides [20, 21].

To understand the action of Epac let us first understand its structure and then its activation process. The structure of Epac consists of mainly 2 regions a regulatory region and a catalytic region. The N-terminal region is termed as regulatory region and the C-terminal region is the catalytic region. The regulatory region has a cAMP nucleotide-binding CNB site in Epac1 there is only one such site but in Epac2 there are 2 sites of binding. Both Epac1 and 2 have a Dishevelled-Egl-10-Pleckstrin it is termed as DEP. The second region or the catalytic region has 2 domains. The first one is the Ras exchange motif termed as REM and the second one is the Ras association termed as RA domain.

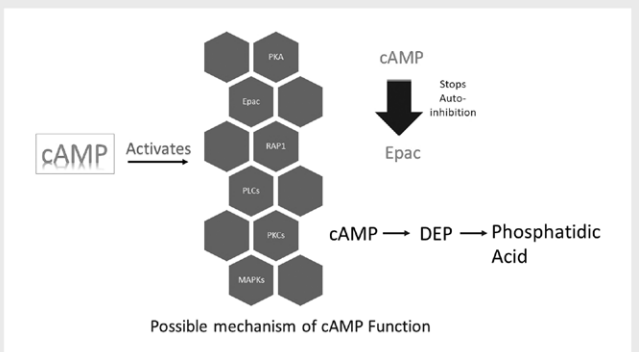
The function of Epac is basically to convert the GDP to GTP. It is the catalyzation process required for the small G proteins, for example, Rap1 and Rap2. The number of processes linked to the activation of Raps is the activation of effector proteins such as Rap1, Phospholipase Cs (PLCs), protein kinase c (PKCs), and MAP kinases (MAPKs). Further research on Epac revealed that the binding of cAMP to the Epacs shows two activities. The first activity is it stops the autoinhibition of Epac and the second activity is that the DEP domains can easily bind to the phosphatidic acid. The outcome of this process is the transportation of Epacs from the cytoplasm into the plasma membrane, this helps in the activation of the Rap1 present inside the membrane [22, 23].

Role of Epac in epinephrine-induced cAMP-PKCε signaling

The protein kinases have an active role to mediate the pain receptor to the higher centers of the brain. It was the efforts of Hucho et al. to study the molecules mediating the cAMP to PKC in signaling. The requirement of DRG neurons was full filled by the adult male rats. This helped to study the translocation of PKC in the neurons. The effect produced due to the epinephrine stimulated β2-adrenergic receptors was the promotion of translocation process of PKC membrane by the epinephrine into the IB4(+) neurons. The PKC translocation was also produced by increasing the levels of cAMP. This increased cAMP was due to the cholera toxin-activated Gαs or by forskolin. This release also activates the acetylcholine and also stimulates the translocation of PKC. The action of CMIQ a potent specific PKA inhibitor does not produce any effect during the epinephrine-induced PKC translocation. The results were conclusive enough to show that the epinephrine was able to produce cAMP-dependent PKC signals produced in the DRG neurons. The activation of Epac is also possible by the 8-pCPT-2-O-Me-cAMP (CPT), which is a selective agonist, and this mimics the action of epinephrine. This continuous observation led to the idea of cAMP-linked PKC signaling which is pivotal of Epac. The other observation led to know a probable reason for the downstream of Epac. The decrease in the levels of phosphatidylinositol (PI) which are specific to PLC and PLD, which are crucial for the activation and translocation of PKC, also decreased the epinephrine and CPT- dependent PKC translocation. Further observation of the Epac towards their behavioral patterns show that the epinephrine and CPT can produce hyperalgesia and can also be inhibited by the PKC inhibitors, εV1–2. As the similarity between the epinephrine and CPT the PI-PLC and PLD have similar functions. Thus, the inhibitors of PI-PLC and PLD affect the functioning of epinephrine- and CPT-induced hyperalgesia [24]. Possible mechanism of action of cAMP function (▶ **Fig. 1**).

Role of Epac in Cognition

Pathology data have suggested that variations in Epac activity levels are interrelated to numerous cognitive diseases. For example, augmented Epac2 levels are found in the hippocampus and prefrontal cortex of depression-related suicides [25]. Furthermore, a genome screen acknowledged Epac2 as an applicant gene for autism. The mRNA level of Epac1 is raised whereas in Alzheimer's patients, the level of Epac2 is suppressed in the hippocampus and frontal cortex of the brain. Recently, Epac-Rap1 signalling is also found to control a key protein in the advancement of Alzheimer's disease. Because memory and learning deficits are the common symptoms of these ailments, the study of Epac's role in memory



▶ **Fig. 1** Different possible mechanisms of cAMP function.

regain is significant to understand the mechanism and to find the treatment of these discrepancies [26].

PGE2-induced Hyperalgesia

Levine and his colleagues studied the PGE2 dependent hyperalgesia. They found that there is an increase in sensitization in the peripheral nociceptor on the hyperalgesia for the stimulus, this is termed hyperalgesia priming [27]. The experiment which was carried out under normal conditions on the rats shows the hyperalgesic effect on the injections of PGE2 to the paw of the hind limb. This effect lasted for less than 4 hours. Even the lower dose of the carrageenan treatment had the signs of inflammation. The signs were inflammation in the hind paw of the rat, redness of the skin, and change in the reaction on the external stimulus such as the decrease in the paw movement for a minimum of three days on the external mechanical stimulus. On the other hand, when the injections of PGE2 was given to the rats after 5 to 21 days the paws show the different hyperalgesic effect. The difference in the hyperalgesia by the PGE2 was the enhancement in the duration of the effect for more than 24 hours. The late phase hyperalgesia which was mediated by the PKA does not show any effect mediated by PKA instead is inhibited by the PKC inhibitor. Accidentally it was found that this phenomenon occurs only in male rats [24].

The differences in the PGE induced hyperalgesia and epinephrine induced hyperalgesia are, in the PGE2 induced hyperalgesia the signaling is carried out by the PKA, PKC, and ERK, whereas in the epinephrine induced hyperalgesia the priming action takes place with the help of or is mediated through PKC signals and do not have any action mediated by the carrageenan treatment. The second major difference is that in the epinephrine induced hyperalgesia cytoskeleton plays a major role, whereas in the PGE2 induced hyperalgesia cytoskeleton comes into the picture only after the carrageenan treatment [24].

Signaling by Epac-PKCε

In the nociception, it is evident that the release of PKC epsilon is the evoke of the pain sensations [28, 29]. The findings by the Gold et al. and Parada et al. was surprising. They found that the signals from the cAMP towards the PKC were without the involvement of PKA. In recent studies, the cAMP did not just activate the PKA but also the Epac which in turn stimulate the activation of PKCε [30]. The description for the increased PGE2 induced hyperalgesia was possible after the study on the activation of P2X3 receptors [24]. P2X receptors are a group of purinoreceptors. The P2X3 receptors are channels of trimeric cations. The activation of P2X3 receptors requires energy and is activated by ATP [28]. The study by Li Yen M Huang and Yanping Gu was on the effects of PGE2 on the P2X3 receptors. The results revealed the transfer of signals into the DRG neurons and α, β-meATP. The transfer of signals shows behavioral responses which were produced under the normal condition and in the inflammatory conditions. The basic functioning of the P2X3 receptors was as the sensory neurons, which transmits the signals from the site of the periphery to the terminal DRG neurons i. e., the spinal cord [24, 28]. Once there is an inflammation or there is an injury to the nerve, ATP activates the P2X3. This results in the behavioral response towards the nociceptive stimulus produced. This activates the upregulation of the P2X3Rs in the DRG neurons. Whereas when there is no stimulus or in the normal conditions PGE2 stimulates the production of signals mediated by P2X3R (I_{ATP}) in DRG neurons [31, 32]. The flinch responses are activated by the stimulations to PKA by the P2X3R. When the test was carried out by injecting CFA to the hind limb paw of the rats, it caused inflammation which increased the production of P2X3R responses initiated by the PGE2 in DRG neurons. The actual increase in the P2X3 responses can be mediated by both the stimulations i. e., by PKA and PKCε. The results also show that the Epac activation mediated by PGE2 was only observed in the CFA treated DRG neurons of Rats [24].

The Expressions of Epac1 and Epac2 in Injury

The work by Vasko et al. suggested that the Epac2 production is increased in the DRG of rats after the inflammation induced by the CFA. And Epac1 production was increased in the mice after the treatment of CFA, this explains that Epac2 is produced in the inflamed cells by the CFA, and Epac1 production increases only after the treatment of CFA. It is commonly observed by many scientific professionals that the increased production of both Epac1 and 2 is seen during the inflammation. The observations also suggest the increased production of the neurons which express Epac1 and Epac2 during injuries [29, 31, 33, 34].

Importance of cAMP (PKA and Epac) in Memory and Signalling

In this article and all other articles studied, the cAMP follows 2 probable mechanisms for its action. The first probable mechanism is the PKA involvement or mediated, whereas the second mechanism requires the Epac. There is evidence that shows that the cAMP alone has a different pattern of signals to retrieve memory in the norepinephrine or epinephrine deficient mice. In this experimentation the interest was to determine the actual mediators and targets i. e., Epac, PKA, or ion channels of cAMP in memory formation and signal transmission. To understand this Ming Ouyang and his team in the year 2008 carried out the experiments by forming highly selective models where the PKA was given priority over Epac and vice versa. The PKA and Epac were selectively stimulated by the help of Sp-6-Phe-cAMPS and Sp-8-pCPT-O-MecAMPS. When the scientists subjected the mice to Sp-6-Phe-cAMPS 30 mins before the test of retrieval after a complete day of training there was no retrieval in the memory except only for the higher doses. This can be easily explained by the retrieval effect produced by the combined doses of 0.2 and 0.5 g of each stimulant respectively. The drug with the dose of 0.5 g of both stimulants was reported with nil response. These data suggested to the scientists that the response towards the retrieval of the memory required both the Epac and PKA to function together in norepinephrine/epinephrine deficient mice [35].

Recent Advancement

cAMP amplification protects hepatocytes in contrast to diclofenac-induced cell death, a process mainly relating to Epacs. The cAMP/

EPAC pathway may be a new target for the treatment of DILI [36]. Epac has the aptitude to encourage or impede cell proliferation, migration/metastasis, and apoptosis in several carcinomas in the brain and other vital organs [37], since EPAC displays a decisive role in vascular pathology and physiology, it could characterize a possible target for drugs designed to treat hypertension and atherosclerosis [38]. As it was stated before, the PKA signalling cascade looks as if over-activated in the prefrontal cortex of elderly animals. Therefore, insignificant activation of the cAMP/PKA signalling cascade with PKA activators and cAMP-specific inhibitors could worsen the cognitive routine related to the prefrontal cortex [39]. Learning yields robust cAMP-dependent plasticity in intrinsic MB neurons, which is prejudiced toward naturalistic reward learning. This advocates that cAMP signalling may help to modulate intrinsic MB responses in the direction of salient stimuli [40].

Conclusion

The brain has various functions to perform. These functions are possible only because of the structures which carry the information from the higher center brain to the response desired site. The transmission of the information in the form of signals was found later when the neurotransmitters came into existence in 1921. Later as the researches increased the understanding of the molecular requirements of the neurons and nervous system was also understood. Later the importance of individual molecular structures was understood. In this article, we have tried to write our understanding towards the Epac activated by the cAMP. The PGE2 mediated hyperalgesia and inflammation require the action Epac for the response. The memory functioning and system are present even in invertebrates, but it is not as well developed as in we human beings, and this developed branch of the nervous system functions as different memories. From the receiving of perceptions at the sensory neuron to delivering it to the higher centers of the brain and then carrying back from the brain to the response just happens in seconds and this lightening movement of the signals is possible only because of the molecular structure which is eternally functional in the nervous system. There are still many molecular structures not discussed in this review and have a prominent role in maintaining our body functions in various ways. The need for the study of the functioning of cAMP and linked molecular becomes much more important as we understand the need for these structures in our body. This article is an attempt to understand a molecular structure linked with cAMP.

Search Strategy

These searches were confined only to the English language. The author has used broad Major Exploded Subject Headings (MesH) terms and keywords [Epac, neural signaling, cAMP, neuron, secondary messenger and PKA] with the following prefix and suffix [role of, pharmacological use, function of, importance of and secondary messenger], with these words we have searched EMBASE, PubMed, PsycINFO, Medline, Google, ScienceDirect search engine. First of all, the papers were collected whose open-access file was available, the abstract was copied from paper that was not accessible. Later following the guideline of Systematic Reviews and Meta-Analyses (PRISMA), the data which were not relevant to the theme of this paper was discarded, the remaining data were characterized according to their heading such as function, Role, Importance. All collected publications were reviewed manually and also checked regarding the references of interest.

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Conflict of Interest

The authors report no conflict of interest regarding authorship or publication of this manuscript.

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