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# *An Update on the Manner Adenylyl Cyclases (ACS) Might be the Therapeutic Targets Regarding Neurodegenerative Diseases (NDD) Treatment: A Review*

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## *Abstract*

*Adenylyl cyclases (ACs) represent vital governers of cyclic adenosine monophosphate (cAMP) signaling—a pathway pivotal i) for neuroregeneration, ii) synaptic plasticity, as well as iii) neuronal survival. In both the central nervous system (CNS), in addition to peripheral nervous system (PNS), damage stimulated, activation of ACs facilitates axonal outgrowth in addition to working rectification via the stimulation i) of proteinkinase A (PKA), ii) exchange proteins directly activated by cAMP (Epac), along with iii) cAMP-response element-binding protein (CREB). Of the variable AC isoforms, calcium-sensitive AC1, AC8, as well as AC5, in addition to bicarbonate-reactive soluble AC (sAC), have advented in the form of crucial modulators of neuroplasticity along with xon regeneration. Such isoforms alignment causes diverse cellular reactions— inclusive of i) gene transcription, ii) cytoskeletal remodeling, as wellas iii) neurotransmitter liberationto i) metabolic, ii) synaptic, in addition to iii) damage correlated signals. Decontrolling of AC action has been involved in the pathophysiology of neurodegenerative diseases (NDD), for instance i) Parkinson's disease (PD), ii) Alzheimer's disease (AD ), along with iii) amyotrophic lateral sclerosis (ALS), Huntingtons disease (HD) in addition to, iv) in chronic pain syndromes. Pharmacological manipulation of cAMP quantities via AC activation, phosphodiesterase (PDE) hampering, or pituitary adenylyl cyclase-activatingpolypeptide (PACAP) receptor signaling has demonstrated therapeutic attraction in preclinical models by i) escalating neurogenesis, ii) remyelination, in addition to iii) synaptic healing. On the other hand, targeted hampering of particular AC isoforms, specifically AC1, has illustrated effectiveness in diminishing maladaptive plasticity as well as neuropathic pain. This review emphasizes the variability in parts of ACs in neuronal working along with damage reactions as well as details genesis of approaches regarding their therapeutic targeting after earlierdetailing PD, AD, ALS, HD regarding their association with Gut Microbiota& Bile Acids (BA). among the elderly population in the community.*

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## Introduction to Cyclic Adenosine Monophosphate (cAMP)-Dependent Signaling in Nerve Regeneration

Nerve regeneration is a critical biological event with intense repercussions in reference to the rectification of working subsequent to inherent damage to the nervous system. Whereas the peripheral nervous system (PNS) illustrates a pronounced capability for self -healing, regeneration in the central nervous system (CNS) is considerably restricted. Such variation takes place secondary to i) both inherent neuronal factors as well as the ii) extrinsic hampering milieu in the CNS. Getting insight regarding existence of such mechanistic modes is imperative for generating therapeutic approaches with objective at facilitating neuroregeneration, particularly in cases of i) traumatic brain damage, ii) spinal cord damage, or iii) neurodegenerative disease (NDD s). At the cellular extent, the failure of CNS neurons to regenerate is partially owing to the existence of hampering molecules for instance i)Nogo-A, ii) myelin-associated glycoprotein (MAG), along with iii) oligodendrocyte-myelin glycoprotein (OMgp), in addition to the generation of a glial scar abundant in chondroitin sulfate proteoglycans (CSPGs), that taken together impede axonal enlargement [1].

Nevertheless, the incapacity of mature CNS neurons to activate an inherent growth program further possesses a central part. Conversely, peripheral neurons react to damage with the i) upregulation of regeneration-associated genes as well as ii) activation of signaling pathways that embrace axonal outgrowth, inclusive of the 3′ ,5′ -cyclic adenosine monophosphate (cAMP) signaling to series. The cAMP pathway is one of the maximum substantially assessed intracellular signaling pathways implicated in axon regeneration. It possesses a pivotal part in translating damage signals into a regenerative reaction. Subsequent to neuronal damage, escalated cAMP quantities get found in peripheral neurons, where they correlate with escalated i) axonal lengthening, ii) branching, as well as iii) target reinnervation. Such regenerative actions of cAMP are basically modulated via i) activation of the protein kinase A (PKA), ii) that phosphorylates transcription factors hampering for instance i) the cAMP- response element-binding protein (CREB), resulting in transcription of regeneration- correlated genes [2,3]. In empirical models, contrived escalating cAMP quantities in CNS neurons has been illustrated to partially tackle their regenerative failure. Such actions got attained either by i) direct implementation of cAMP analogs for instance dibutyryl-cAMP or via ii) pharmacological hampering of phosphodiesterases (PDEs), which degrade cAMP. For example, delivery of rolipram, a phosphodiesterase 4 (PDE4) hampering agent, leads to maintained cAMP signaling as well as has been correlated with improvements in axon regrowth as well as working rectification subsequent to spinal cord damage [4].

Additionally, cAMP works synergistically with neurotrophic factors for instance the i) brain-derived neurotrophic factor (BDNF) in addition to ii) nerve growth factor (NGF), escalating their actions on axon expansion, along with survival. cAMP signaling further impacts cytoskeletal remodeling, growth cone dynamics, in addition to the expression of integrins— pivotal constituents in axonal guidance, along with substrate crosstalk. Further than PKA, exchange proteins get directly activated by cAMP (Epac), that modulate small GTPases for instance Rap1 as well as Rac1, further assisting in axon lengthening, in addition to balance trajectory growth. Such sophisticated downstream signaling accounts for cAMP to an aligned regenerative reaction that incorporates metabolic, structural, gene expression alterations [5,6]. Significantly, the source of as well as controlling of cAMP amongst neurons are intricately regulated by adenylyl cyclases (ACs)—enzymes that catalyze the transformation of adenosine triphosphate (ATP) into cAMP. In mammals, nine membrane-bound AC isoforms (AC1–AC9) in addition to one soluble isoform (sAC or AC10) are acknowledged. Every isoform document unique controlling characteristic in addition to escalating tissue organizations, along with pronouncedly expressed in the nervous system. Noticeably, calcium/calmodulin-sensitive isoforms, for

instance AC1 as well as AC8, are activated in reaction to neuronal action in addition to possess a significant pivotal part in synaptic plasticity, along with memory generation. Their implications in activity- based cAMP enables them in the form of promising targets for escalating neuroregeneration in a damage - reactive fashion [7,8]. The soluble adenylyl cyclase, that is activated by bicarbonate as well as intracellular pH alterations, has launched in the form of a plausible metabolic sensor amongst neurons (Figure 1) [rev in 9].

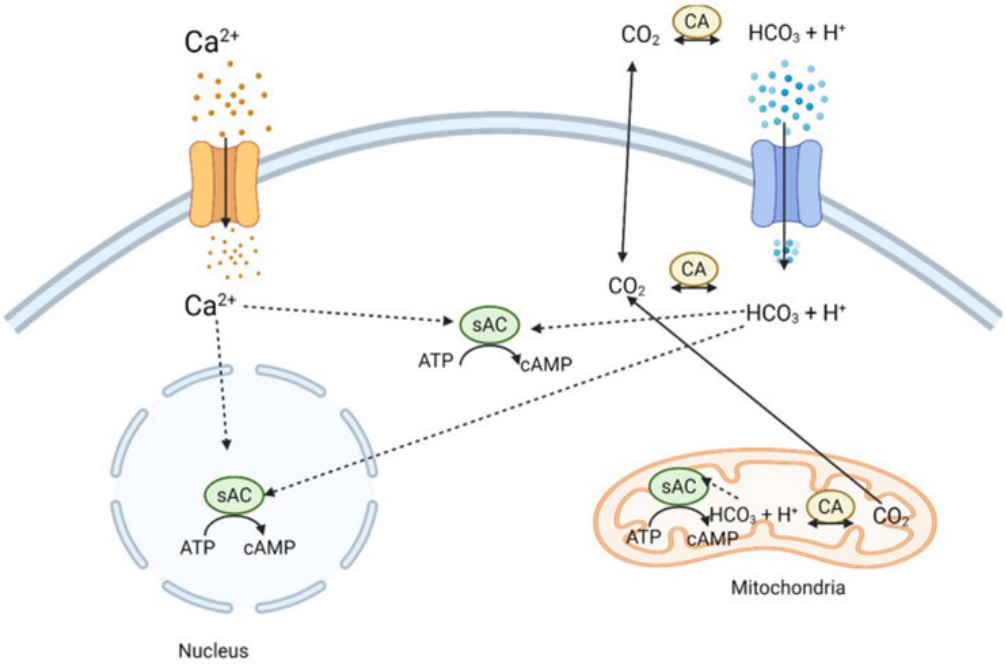


**Figure1:** Courtesy ref no-9-Diagram illustrating the key regulatory and activation mechanisms of soluble adenylyl cyclase (sAC) in a eukaryotic cell. sAC, located in the cytosol, nucleus, and mitochondrial matrix, is activated by calcium ions (Ca2+) and bicarbonate (HCO3−). The influx of Ca2+ stimulates sAC in the cytosol and nucleus to produce cAMP from ATP. Bicarbonate, generated from carbon dioxide (CO2) by carbonic anhydrase (CA) or transported into the cell, activates sAC in the cytosol and mitochondria. In the nucleus, sAC-dependent cAMP can regulate transcription, while in the mitochondria, it influences metabolism and mitochondrial dynamics. Created in BioRender. Tomczak, J. (2025) https://BioRender.com/mt2mtgo.

Its activity associated cellular energy state to cAMP generation in addition to downstream signaling, yield variable mechanistic modes by which metabolic stress or damage - stimulated alterations in intracellular situations possess the capacity of affecting regeneration. Addition of a further layer of complicated nature as well as plausibility for therapeutic targeting, in the form of manipulation of sAC possesses the capability of plausibility of escalating regeneration by synchronizing energy metabolism with growth- facilitating signaling series. Further corroboration for the part of cAMP in regeneration stems from studies where utilization of acquired disfigurement models, where an earlier damage to the peripheral branch of a dorsal root ganglion (DRG) neuron escalates the capability of its central branch to regenerate amongst the spinal cord [10,11]. Such occurrence is correlated with a sustained escalation in cAMP quantities as well as upregulation of regeneration- correlated genes, buttressing the central part of the cAMP pathway in beginning in addition to sustenance of a growth proficiency - state. Although such advancements have taken place, successful translation of cAMP- dependent therapies into clinical practice continues to be bothersome in view of variable concerns for instance transient actions, ii) absence of isoform specificity, along with iii) plausible inimical sequelae of systemic cAMP escalation. Thereby, future research needs to be escalatingly concentrated on targeting particular AC isoforms that possess enrichment in neurons as well as activated under regenerative situations. Getting insight into the manner every AC isoform assist in regeneration, both in case of normal in addition to pathological situations, would be crucial to fashion exactitude, along with efficacious therapies [7,12].

Earlier we reviewed etiopathogenesis of Amyotrophic Lateral Sclerosis with specific emphasis on Gut Microbiota (GM) enteric nervous system (ENS) and associated crosstalk of astrocytes, GM, Muscle with mitochondrial melatonergic pathway, part of‘Iridoids. (Monotepenes) and Other natural products for development of potential therapies in alzheimer’s disease, part of dietary fatty acids and GM development of neurodegenerative diseases (NDD). Role of Bile Acids in Neurological Functions and NDD development, role of mitochondrial transport in etiopathogenesis & management of various CNS diseases, neurodegenerative diseases, immunometabolic diseases, cancer, viral infections, Brain organoids controversy regarding the COVID19 Infection causing Neurodegeneration ,new Parkinson’sdiseaseor its acceleration remains unresolved, Role of CD4+T Helper Cells as Mediators of Inflammation in the Pathophysiology of Multiple Sclerosis[13-20].Here we have attempted to highlight Role of ACs in management of various NDD.

## Adenylyl Cyclase in Neuroplasticity

Neuroplasticity, the brain’s capacity of modifications of its structure as well as working in reaction to damage encountered, or disease, is an elemental characteristic that lies beneath i) learning, ii) memory, iii) sensory transformation, in addition to iv) rectification from neural damage [21]. Such events take place at plethora of magnitudes, varying from molecular along with synaptic alterations to large-scale cortical redistribution [22]. One of the pivotal mechanistic modes of neuroplasticity is i) synaptic plasticity, that pointed to the capability of synapses to reinforce or escalate inimicality with time in reaction to activity. Synaptic plasticity is widely categorized into i) short-term as well as ii) long-term plasticity. I)Short-term plasticity implicates transient modifications in synaptic buttressing, canonically staying milliseconds to minutes, in addition to is mainly modulated by alterations in presynaptic neurotransmitter liberation. Conversely, long-term plasticity, for instance long-term potentiation (LTP) along with long-term depression (LTD), results in persistent modifications in synaptic efficacy, as well as is believed tobe the cellular ground of learning, memory, in addition to encounter-based adjustment [23]. LTP definitions portray perpetual escalation in synaptic buttress subsequent to high-frequency triggering of presynaptic neurons. Such occurrence has been substantially assessed in pivotal brain site for instance the i) hippocampus, ii) anterior cingulate cortex (ACC), in addition to the, iii) amygdala [24]. The stimulation of LTP needs calcium influx, that takes place basically via N-methylD-aspartate (NMDA) receptors, along with in certain cases, via L-type voltage-gated calcium channels (L-VDCCs) [25]. The escalation in intracellular calcium triggers a series of molecular processes that results in synaptic buttressing, inclusive of activation of calcium/calmodulin (CaM)- based signaling pathways enrollment, of 2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl) propanoic acid receptors (AMPARs) to the synaptic membrane, as well as structural manipulation of dendritic spines [26].

At the molecular extent, long-term synaptic plasticity is controlled by complicated nature intracellular signaling pathways which translate synaptic activity into enduring working as well as structural alterations. One of the crucial signaling molecules in such event is cAMP, ii) a second messenger which possesses a pivotal part in activity- based neuronal modifications (Figure 2).

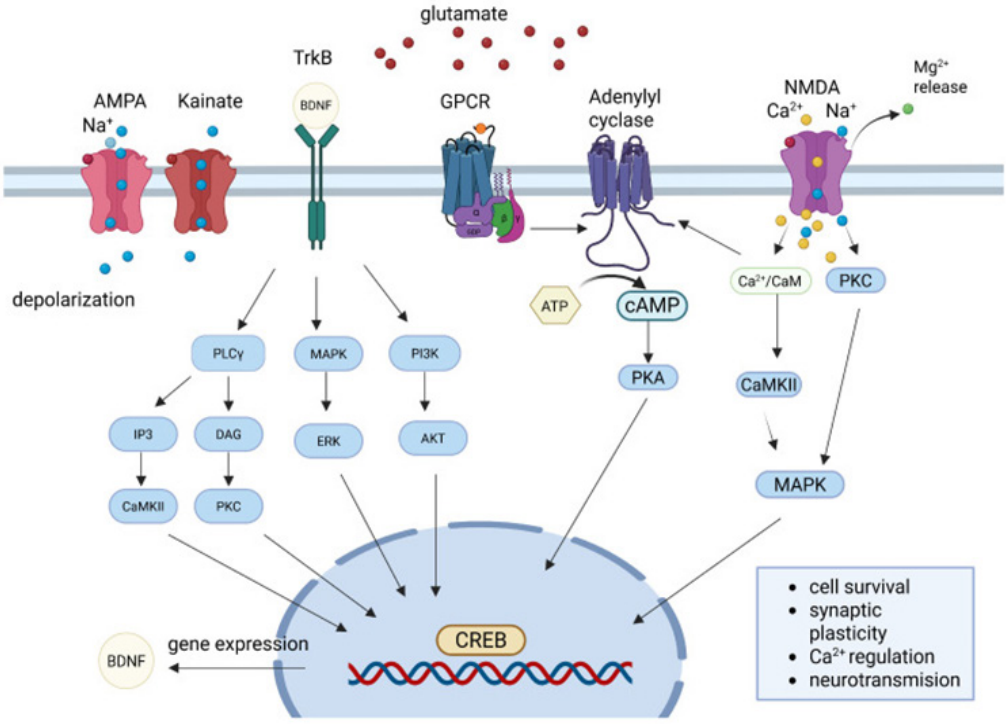


**Figure2:** Courtesy ref no-9--cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA)/cAMP-response element-binding protein (CREB) and brain-derived neurotrophic factor (BDNF) signaling pathways involved in synaptic plasticity. Synaptic activity triggered by glutamate release activates ionotropic receptors-AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid), NMDA (N-methyl-D-aspartate), and kainate-as well as GPCRs (G-protein-coupled receptors), leading to membrane depolarization and calcium ion (Ca2+) influx. GPCR stimulation enhances cAMP production via adenylyl cyclase (AC), activating PKA, which phosphorylates CREB. In parallel, BDNF binding to tropomyosin receptor kinase B (TrkB) receptors activates mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK), phosphoinositide 3-kinases (PI3K)/AKT, and phospholipase C gamma (PLCγ) pathways, which also converge on CREB. Activated CREB drives transcription of genes essential for synaptic plasticity, including BDNF itself. These signaling cascades regulate key processes such as synapse strengthening, calcium homeostasis, neurotransmission and neuronal survival. Created in BioRender. Tomczak, J. (2025) https://BioRender.com/mt2mtgo.

cAMP in addition to its downstream effector, CREB, possesses pivotal part in synaptic plasticity, i) especially in the generation, along with ii) sustenance of LTP, an elemental mechanistic mode that lies beneath learning along with memory. Subsequent to synaptic triggering, escalated quantities cAMP activates PKA, that phosphorylates CREB at serine 133. Such manipulation allows binding of CREB to cAMP response elements (CRE) in the promoters of target genes, starting transcription. The expression of such genes is imperative for forming i) proteins implicated in synapse generation, ii) dendritic spine remodeling, as well as iii) long-term memory consolidation [27]. Empirical models embrace the central part of CREB in neuroplasticity. i) Mice expressing a dominant-negative form of CREB illustrate insufficiency in LTP in addition to long-term memory, whereas the ii) ones overexpressing active CREB exhibit escalated synaptic buttressing in addition to improvement of memory working [28,29]. Apart from, i) facilitating gene expression imperative for synaptic growth, ii) CREB further manipulates neuronal excitability, along with iii) incorporates variable signaling inputs over passage of time, therefore assisting in both the encoding as well as recovery of memory traces [30,31]. Additionally, CREB activity promotes the expression of BDNF, a crucial mediator of synaptic reinforcing in addition to neuronal survival [32,33].

In the hippocampus, NMDA receptor activation results in calcium influx, that induces calcium/calmodulin-

dependent AC activity, therefore facilitating cAMP generation. Such signaling pathway is pivotal for the induction as well as sustenance of LTP, inlieu of it promotes the molecular alterations needed in reference to long-term synapticmanipulat ations [7,34]. The cAMP stepwise patterns further crosstalks with voltage-gated calcium channels, forming a feedback loop which also augments the calcium influx as well as escalated synaptic heightening. Such mechanistic modes are found in plethora of hippocampal pathways, inclusive of i) the Schaffer collateral, ii) mossy fiber, in addition to iii) medial perforant pathways, where AC1, along with iv) AC8 cooperate to promote memory consolidation [35,36].

B.Adenylyl cyclase further possesses a pivotal part in cortical plasticity, specifically in the ACC, i) where synaptic modifications assisting in sensory procedure proceeding, ii) learning, in addition to iii) pain discernment [37,38]. Both AC1, along with AC8 aids in synaptic heightening in the ACC, i) however AC1 possesses a greater pronounced part in NMDA receptor- based LTP [39]. Acknowledged its greater sensitivity to calcium, AC1 works in the form of a main calcium sensor for the NMDA receptor as well as L-VDCC- manipulated signaling in ACC neurons. The cAMP generation that results there in, stimulates downstream pathways which embrace LTP stimulation in addition to sustenance, strengthening the part of AC1 in the form of a central controller of synaptic plasticity [38. 40,41,]. AC1 is necessary for cortical generation, along with sensory proceeding. Studies that used AC1 knockout models have documented significant aberrations in the working maturation of thalamocortical synapses as well as changes in the barrel cortex cytoarchitecture, pointing that AC1 is essential for suitable sensory circuit [,42,43]. Moreover, AC1 has been held responsible in encounter - based plasticity in the thalamus, where it helps in the buttressing of whisker relay synapses in reaction s to sensory input [44].

Further than its part in normal plasticity, adenylyl cyclase- modulated signaling is crucially implicated in damage - stimulated neuroplasticity, specifically in situations for instance chronic pain. Subsequent to nerve damage, synaptic communications in the ACC go via maladaptive alterations which aids in the continuation of pain. Such damage - stimulated manipulations implicate both presynaptic as well as postsynaptic changes, inclusive of escalated glutamate liberation, enhanced AMPA receptor- modulated reactions, in addition to upregulated phosphorylation of glutamate receptor 1 (GluR1) subunits [45-47]. AC1 has been isolated in the form of a pivotal governer of synaptic plasticity in chronic pain situations, in view of its actions is needed for the induction of LTP in variable brain areas [37, 38, 48]. In the ACC, a pivotal area implicated in discernment of pain, AC1 modulates both presynaptic, along with postsynaptic plasticity subsequent to peripheral nerve damage. Escalated AC1 actions results in escalated presynaptic glutamate liberation as well as upregulation of postsynaptic AMPA receptor reactions in layer II/III neurons of the ACC, aiding in long-term pain sensitization [48]. Studies have illustrated that AC1 knockout mice demonstrate how significant reductions in neuropathic pain- associated synaptic heightening, further embracing the pivotal part of AC1 in augmenting pain- associated plasticity in the ACC [49,50]. The capacity of AC1 to couple calcium signaling to cAMP generation enables it to act in the form of a central actor in both kinds of LTP, guiding synaptic modifications that lie beneath chronic pain [48,51]. Pharmacological hampering of AC1 has been illustrated to i) result in avoidance of pain- associated synaptic heightening, ii) barricade behavioral sensitization, in addition to iii) diminish damage- stimulated anxiety [51]. Separate from broad-spectrum cAMP modulating agents, AC1 hampering agents selectively interfere with maladaptive plasticity whereas conserving normal synaptic working, which enables them tobe promising candidates for therapeutic arbitrations in chronic pain, along with associated situations [51,52]. The selective AC1 hampering agent NB001 has been illustrated to i) efficaciously barricade LTP stimulation in the ACC as well as ii) insular cortex without influencing their basal synaptic transmission, demonstrating its plausibility for selectively targeting maladaptive plasticity whereas conserving normal synaptic working [48,53]. Whereas AC1 is the dominant actor in damage- stimulated plasticity, AC8 further aids in synaptic modifications, despite although its working apparently possesses greater specialization. Separate from AC1, that is substantially sensitive to calcium influx as well as needed for NMDA receptor- based LTP, AC8 is implicated in i) forskolin- stimulated heightening in addition to ii) synaptic deintensification [37-39]. In neuropathic pain models, AC8 mRNA expression escalates in the ACC, iii) pointing that it might possess

a part in sustenance of damage - stimulated plasticity [37].

## Adenylyl Cyclase Signaling in Axonal Regrowth along with Nerve Healing

Adenylyl cyclases possesses a central part in the controlling of axonal outgrowth by generating cAMP implicated in plethora of cellular events, inclusive of i) neurite expansion, ii) growth cone dynamics, as well as iii) axon regeneration. Among the AC family, soluble adenylyl cyclase(sAC) has received extensive interest in the form of a pivotal modulator of axonal growth [11]. sAC has been illustrated to possess a critical part in retinal ganglion cell (RGC) survival in addition to axon regeneration. Its activation, either via physiological stimuli, for instance electrical action or direct overexpression, meaningfully escalates i) axon growth, along with ii) neuronal survival both in vitro as well as in vivo. Conversely, the hampering of sAC drastically diminishes such regenerative results, buttressing its necessary part. Noticeably, transmembrane AC isoforms AC1 in addition to AC8 are not needed for such actions, indicating that sAC is the pronounced facility of cAMP implicated in such regenerative pathways [54,55]. sAC-generated cAMP is especially efficacious at facilitating neurite outgrowth on hampering substrates, for instance CNS myelin [10]. For instance, sAC is i) imperative for the BDNF-modulated tackling of MAG- stimulated hampering, along with ii) escalating sAC quantities in neurons adequately facilitates axonal growth on myelin in vitro as well as regeneration in vivo. It emphasizes sAC in the form of a critical intracellular transducer which possesses the capability of transforming extracellular growth hints into pro-regenerative cues via cAMP development [56,57]. Netrin-1 signaling further has convergence with sAC-modulated pathways i) at the time of axonal formation in addition to ii) regenerative axon growth. Netrin-1 is a bifunctional guidance tip which possess the capacity of attracting or repelling axons at the time of neural formation, on the basis of receptor background [58-60]. Such bifunctionality gets manipulated by two receptor families: i) DCC (Deleted in Colorectal Cancer) as well as ii) UNC-5 homologues [61,62]. Netrin-1 is implicated in variable events, inclusive of i) axon branching, ii) guidance, in addition to iii) peripheral nerve regeneration. In generating cortical neurons, netrin-1 drastically escalates axon branching via calcium transients that activate the downstream effectors i) calcium/calmodulin- based protein kinase II (CaMKII) , along with ii) mitogen-activated protein kinase (MAPK) [63]. Wu et al. (2006) [64], illustrated that sAC is expressed in generating rat axons in addition to generates cAMP reaction s to netrin-1. Overexpression of sAC i) facilitated axonal outgrowth as well as ii) growth cone evolution, iii) whereas its hampering reppressed netrin-1- stimulated reactions, suggesting that, sAC might modulate pivotal part of netrin-1- based axon development [64]. Nonetheless such part continues to be controversial. Moore et al. (2008) [58], documented just inimical sAC expression in embryonic neurons as well as found normal axonal pathfinding in sAC-null mice, implying that sAC is not imperative for all netrin-1- modulated guidance working [58]. Such debatable observations indicate that the aiding in sAC to netrin-1 signaling might be i) circumstance or ii) cell- kind - based or iii) that there is existence of remunerating mechanistic modes. Further than sAC, particular transmembrane adenylyl cyclase isoforms further possess a pivotal part in controlling axonal growth along with neuronal working. AC6 possesses a hampering part in neurite expansion via its crosstalk with the Snapin–SNAP-25 complex, which is essential for liberation from neurons (neurosecretion) in addition to neurite enlargement. Synaptosomal-associated protein-25 (SNAP-25), a crucial constituent of the SNARE complex, promotes synaptic vesicle exocytosis, along with embraces neurite outgrowth [65-68]. Binding of SNAP-associated protein (Snapin) with SNAP-25, escalates its crosstalk with synaptotagmin, which causes stabilization of liberation prepared vesicles in addition to modulates the event of liberation from neurons. The existence of Snapin is pivotal for calcium- based exocytosis, as well as it lacks importantly diminishes exocytotic actions in cells, for instance chromaffin cells [69].

The i) overexpression of AC6 reppresses neurite outgrowth, ii)) whereas its knockdown or disturbance of its interaction with Snapin promotes neurite enlargement. iii This suggests that AC6 controls neurite growth by modulating the Snapin–SNAP-25 complex, probably via cAMP signaling pathways which affect the dynamics of synaptic vesicle liberation as well as neurite development [70]. The expression of SNAP-25 is controlled by transcription factors, for instance the Brn-3a transcription factor, that is key for suitable neurite outgrowth [71.

Furthermore, SNAP-25 expression is generationally controlled in neurons, with greater quantities found in immature neurons as well as diminishes in adult hippocampal hampering synapses [72,73]. Various isoforms of SNAP-25, inclusive of i) SNAP-25a, ii) SNAP-25b, in addition to iii) SNAP-23, aid in various neuronal working, inclusive of i) cell survival, ii) dendritic arborization, along with iii) neurotransmitter liberation [66,74]. AC5 further possesses a vital part in coordinating purinergic signaling at the time of axonal lengthening. It works in the form of a crucial incorporator of the actions elicited by various purinergic receptors, pronouncedly the P2Y1, P2Y13, pivotal as well as P2X7 receptors. Such receptors possess contrasting parts in axonal growth, i) with P2Y1 facilitating lengthening in addition to ii) P2Y13/ P2X7 hampering it. Recent studies point that AC5 possesses a crucial part in orchestrating the actions of such receptors, mainly by manipulating downstream signaling pathways which impact axonal growth. On the hampering of P2X7 receptor, axonal prolongation is escalated via the activation of plethora of vital signaling pathways, inclusive of i) CaMKII, ii) focal adhesion kinase (FAK), along with iii) phosphoinositide 3-kinases (PI3K), that aids in i) cytoskeletal redistribution in addition to ii) expansion, along with the iii) facilitation of axon branching as well as iv) expansion [75,76]. The capacity of AC5 to incorporate such signals reinforces its part in the form of a vital modulator of purinergic regulation over axonal growth. By coordinating the effects of growth-facilitating (P2Y1) in addition to growth- hampering (P2Y13, along with P2X7) receptors, AC5 guarantees the fine-tuned controlling of axonal lengthening [75, 77].

In the background of nerve damage, ACs aids in to meaningfully regeneration in both central as well as peripheral systems. cAMP is imperative for i) self-recovery, ii) axon regeneration, in addition to iii) remyelination healing [78]. The actions of cAMP are transcription based -, modulated via PKA as well as CREB activation, resulting in the upregulation of pro-regenerative genes. Such genes are inclusive of i) arginase I, ii) interleukin-6, the secretory leukocyte protease hampering in addition to iii) metallothionein-I/II, which have illustrated plausibility of tackling myelin- modulated hampering [79]. The activation of ACs at damage region, along in regenerating nerve cues indicate their implications in conditioning the local environment for effective nerve healing [79,80] (Figure 3).

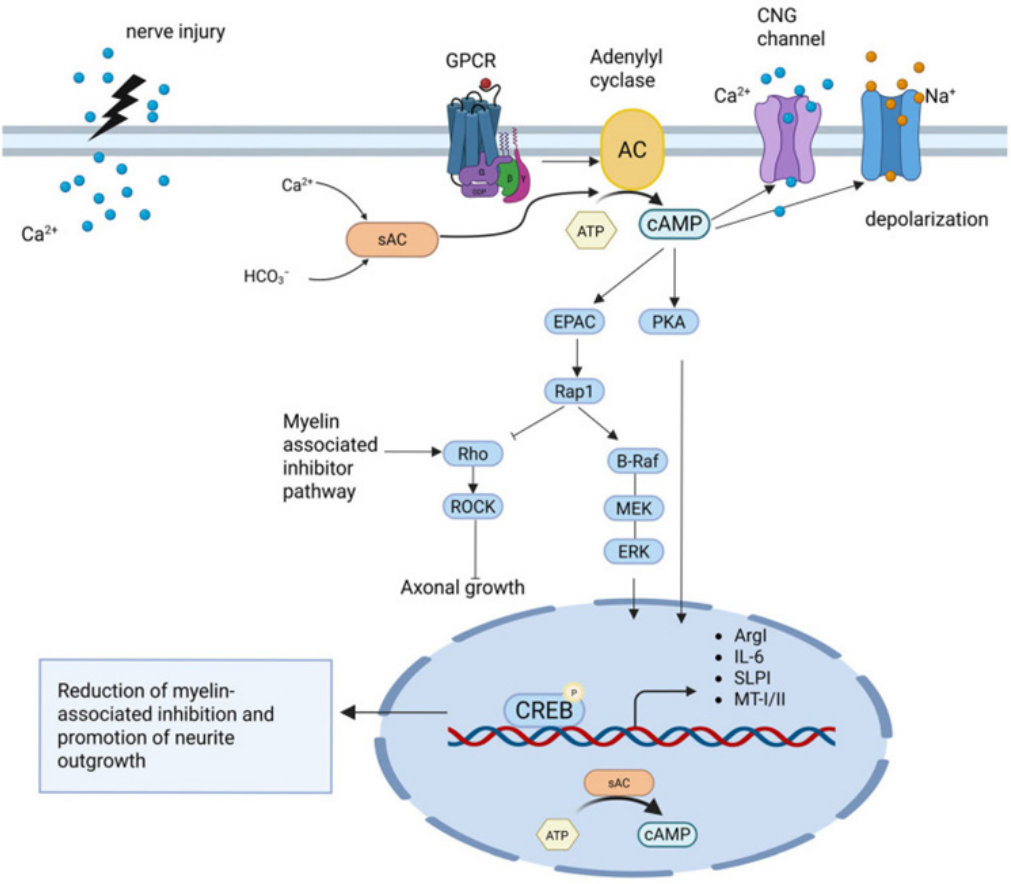

**Figure3:** Courtesy ref no-9--cAMP-mediated signaling pathways promoting axonal regeneration after nerve injury. Nerve injury leads to calcium influx and activation of G-protein-coupled receptors (GPCRs), which stimulate transmembrane adenylyl cyclases (ACs) and soluble AC (sAC) to produce cAMP. Elevated cAMP levels activate two major effectors: protein kinase A (PKA) and exchange protein directly activated by cAMP (Epac). PKA phosphorylates the transcription factor cAMP-response element-binding protein (CREB), promoting the expression of regeneration-associated genes, including arginase I (Arg1), interleukin-6 (IL-6), secretory leukocyte protease inhibitor (SLPI), and metallothionein I/II (MT-I/II). These genes help overcome myelin-associated growth inhibition. In parallel, Epac activates Rap1, which promotes axonal growth through inhibition of the RhoA/Rho-associated kinase (ROCK) pathway and the activation of the B-Raf/MEK/ERK (MAPK) cascade. cAMP signaling also enhances calcium entry via cyclic nucleotide-gated (CNG) channels, contributing to membrane depolarization and further amplifying regenerative responses. Collectively, these pathways reduce extrinsic inhibitory signals and support intrinsic neurite outgrowth and functional recovery. Created in BioRender. Tomczak, J. (2025) https://BioRender.com/mt2mtgo.

In the central nervous system (CNS), ACs possesses a pivotal part in spinal cord injury (SCI) rectification by controlling i) neuroplasticity ii), axonal regeneration, as well as iii pain mechanistic modes. Of the various AC isoforms, calcium-sensitive AC1 in addition to AC8 have been isolated in the form of critical controllers of both SCI rectification, along with neuropathic pain. AC1, particularly, is key for corticospinal tract development as well as healing, owing to its insufficiency changed corticospinal motor neuron magnitude as well as escalates locomotor rectification following SCI. This points that AC1- modulated cAMP signaling might impact motor circuit reorganization in addition to working rectification [81]. AC1 further assists in neuronal signaling in the spinal dorsal horn, where it promotes extracellular signal-regulated kinase (ERK) activation —a pathway involved in spinal sensitization along with the continuation of pain subsequent to SCI [82]. Furthermore, AC1 along with AC8 control cAMP- based signaling in the ACC, a site implicated in pain discernment as well as emotional reactions to damage. Intriguingly, whereas AC1 expression continues to be unaltered subsequent to nerve damage, AC8 mRNA is meaningfully s upregulated in NMDA receptor 2B-positive neurons in the opposite ACC, pointing a plausible part in synaptic remodeling as well as the generation of neuropathic pain [37].

AC activation has been illustrated to facilitate neuroprotection in addition to regeneration after SCI. Pharmacological strategies that escalate intracellular cAMP, for instance the delivery of meglumine cyclic adenylate, have been i) illustrated to result in improvement in neurological working by activating AC3 as well as ii) repressing phosphodiesterase 4D (PDE4D), iii) therefore escalating axonal regrowth in addition to iv) working rectification [83,84].Moreover, spinal cord transection leads to escalated dopamine-activated AC sensitivity, points to involvement of ACs in i) normal spinal working along with ii) plausible neuroleptic drug inimical sequelae [85]. Recent research further points that targeting the cAMP effector exchange protein directly activated by cAMP 2 (Epac2) possesses the capability of working in the form of an innovative approach i) for facilitating spinal cord healing, ii) owing to Epac2 affects cytoskeletal dynamics as well as iii) cellular adhesion— events vital for neuronal regeneration subsequent to damage [86]. Such observations also embrace the therapeutic implementation of AC manipulation in neural healing. Subsequent to SCI, continued spontaneous action in primary nociceptors is sustained by scaffolded AC in addition to PKA complexes, specifically AC5 as well as AC6, which crosstalk with the A-kinase anchoring protein 150 (AKAP150). Such continued excitability is thought to help in central sensitization, a mechanistic mode lying beneath chronic pain. Additionally, SCI results in i) escalated AKAP150 expression as well as ii) changed AC controlling, with iii) escalated calcium–calmodulin triggering in addition to iv) diminished Gαi hampering of AC action, further augmenting pain signaling pathways [87].

Recent observations points that the perinuclear scaffold mAKAP (alias AKAP6) is i) greater intricately correlated with neuroprotection, along with, ii) axon growth. Such perinuclear cAMP chamber gets controlled by local Ca2+ signaling, which modulates activity- based cAMP escalation as well as following PKA activation [88].

Significantly, genetic elimination of mAKAPα or disturbance of its correlated cAMP signaling results in dysfunction of the neuroprotective actions of neurotrophic factors as well as cAMP escalation, whereas escalating mAKAPα- correlated cAMP signaling escalated RGC survival in addition to axon growth, both in vitro, along with in vivo [4,89]. More recently, mAKAPα was illustrated to control calcineurin/MEF2 signaling to guide activity-- based axon lengthening in hippocampal neurons [90].

Recent studies have emphasized the pivotal part of ACs in optic nerve regeneration. sAC acts in the form of a basic facility of cAMP, aids in BDNF to overcome MAG- modulated hampering of neurite outgrowth. In vitro studies demonstrate that directly escalating sAC quantities in neurons is adequate regarding inducing neurite outgrowth on myelin substrates, whereas in vivo experiments demonstrate that sAC activation facilitates axonal regeneration [57]. Additionally, sAC is reactive to bicarbonate as well as cations, pointing that it serves in the form of a i) metabolic in addition to ii) electrical sensor, incorporating physiological signals to estimate if a neuron survives or regenerates subsequent to damage [11]. Recent research has isolated the AC8 family member Ac78C in the form of a pivotal governer of cAMP generation subsequent to dendritic damage in Drosophila neurons. Ac78C serves downstream of voltage-gated calcium channels to facilitate timely starting of dendrite regeneration. Accrual of calcium, along with cAMP in the cell body takes place subsequent to both dendrite as well as axon damage. Two voltage-gated calcium channels (L-Type in addition to T-Type) are needed for the calcium influx in reaction to dendrite damage, along with possessa part in the swift beginning of dendrite regeneration. The adenylyl cyclase Ac78C is needed for cAMP generation subsequent to dendrite damage as well as timely starting of regeneration in addition to such cAMP generation is based on the calcium influx modulated by the VDCCs [91]. Such observations correspond with earlier studies on mammalian AC8, that is acknowledged to be induced by calcium-bound calmodulin [92]. Activation of the cAMP pathway activates synapses which are silent at rest, whereas the hampering of cAMP signaling silenceing of synapses which were basally active. The Ca2+-sensitive adenylyl cyclase isoform AC8, however not AC1, possesses the specifically significant part regarding rectification of synaptic working subsequent to robust presynaptic silencing [93].

In peripheral nerve damage, AC action is dynamically controlled, affecting the regenerationevent. Subsequent to nerve damage, AC activity escalates at the site of damage and in regenerating axons, specifically in inured - disfigurements nerves where an extra damage had earlier taken place. Such pretoning action is associated with escalated cAMP quantities in nerve segments distal to the disfigurement, indicating a part in escalating axon lengthening along with working rectification [80,94]. Apart from neurons, other cells for instance, i) macrophages, ii) Schwann cells, iii) astrocytes, iv) microglia, as well as iv) endothelial cells, further illustrate AC action near the damage region, suggesting a wider implication in the regeneration events [78]. The regenerative capability of peripheral nerve depends on a series of molecular processes, inclusive of i) calcium signaling, ii) transcription factor activation, iii) inflammation, in addition to, iv) the expression of neurotrophic factors. cAMP is a vital molecular decider in such event, affecting both neurons along with Schwann cells to guide axonal regrowth as well as reinnervation [95]. Nevertheless, peripheral nerve damage usually results in diminished cAMP quantities in view of diminished AC action in addition to escalated phosphodiesterase-modulated cAMP breakdown [5,96]. Such diminishing in cAMP might result in dysfunctional regenerative events, emphasizing the significance of therapeutic strategies with the objective of rectification of AC action or hampering cAMP degradation to escalate rectification.

## Implications of AC Modulation in Neurodegenerative Diseases

Recent research has escalatingly highlighted the pivotal part of adenylyl cyclases in the pathogenesis of as well as plausible therapy of neurodegenerative diseases (NDD). In case of NDD , for instance i) Parkinson's disease (PD), ii) Alzheimer's disease (AD), iii) amyotrophic lateral sclerosis (ALS), iv) spinal muscular atrophy (SMA), in addition to v) spinobulbar muscular atrophy (SBMA), escalating corroboration, points that changes in AC action—if i) isoform particular, ii) spatial, or iii) stimulus- based— possesses a central part in disease propagation to action as well as might act in the form of an attractive therapeutic target. 4 A.In case of PD,

disturbance in cAMP signaling have been reported at plethora of magnitudes. One of the maximum stressing observations is the decontrolling of soluble adenylyl cyclase in parkin-mutant fibroblasts, where basal cAMP quantities are importantly escalated. Such escalation apparently comes from both i) escalated sAC action as well as ii) diminished action of phosphodiesterase 4 (PDE4) [96,97]. Parkin, an E3 ubiquitin ligase, has been illustrated to control mitochondrial calcium homeostasis by facilitating the proteasomal degradation of the mitochondrial calcium uptake 1 (MICU1), a governer of the mitochondrial calcium uniporter(a type of membrane transport protein that facilitates the movement of a single type of molecule or ion across a cell membrane in one direction down the gradient of concentration) [96, 98,rev buy us in ref 99]. Lack of parkin, escalated MICU1 stability that results in raised mitochondrial calcium uptake, that might activate sAC in the form of a remunerating reaction to ameliorate mitochondrial oxidative stress (OS). It stimulates a feedback loop where escalated cAMP in addition to PKA action transitionally raises mitochondrial working by phosphorylating the constituents of the electron transport chain, specifically complexes I along with IV. Nonetheless, chronic activation of such pathway possesses the capacity of resulting in reactive oxygen species (ROS) overgeneration as well as further oxidative injury [96,100]. Correspondingly, animal models of PD further reinforce the germaneness of AC modulated - cAMP signaling. Exposure In a Drosophila model to the mitochondrial toxin rotenone, selective activation of Gαs-coupled receptors in dopaminergic neurons takes place — i) that triggers AC action in addition to ii) enhances intracellular cAMP— iii) redeemed locomotor deficiencies , along with iv) results in avoidance of dopaminergic neuron degeneration, while the activation of Gαi-coupled receptors— i) which hamper AC activity ii) in addition to diminish cAMP— aggravated neurodegeneration [101]. Additionally, pharmacological hampering of PDEs, that breakdown cAMP, are protective to dopaminergic neurons, further highlighting the therapeutic probability of boosting cAMP signaling in PD [102,103]. At the magnitude of the basal ganglia circuitry, the significance of AC5, a transmembrane AC isoform, assumes specifically obviousness. AC5 is pronouncedly expressed in dopaminergic target regions for instance the striatum, where it incorporates D1 along with D2 receptor signaling in medium spiny neurons [104]. Elimination of AC5 in knockout mice results in motor insufficiencies simulating parkinsonian symptoms, inclusive of i) bradykinesia as well as ii) might result in dysfunctional alignment, indicating that other AC isoforms for instance AC1 or AC6 do not possess the capacity of totally remunerating AC5 working [105]. Intriguingly, the hampering of AC5 apart from influencing baseline motor control, but further possess a part in modulating L-DOPA-stimulated dyskinesia (LID). In models of LID, AC5 hampering, diminishes PKA actions as well as downstream targets for instance FosB/ΔFosB, which are involved in the maladaptive plasticity correlated with chronic L-DOPA treatment [105,106]. The therapeutic probability of manipulating AC action is also exhibited by studies targeting A2A adenosine receptors, that are coexistent - with D2 dopamine receptors in the striatum in addition to couple with Gs proteins. The A2A receptor activation i) reduces D2 receptor signaling, along with ii) indirectly induces AC action; antagonists of A2A receptors escalate D2 receptor working, decrease AC5 activation along with results in improvements in motor symptoms, yielding an alternative or commensurable strategy to dopamine replacement treatment [107–109]. Furthermore, governers of AC5, for instance i) protein phosphatase 2 catalytic subunit beta (PPP2CB) as well as ii) NSF attachment protein alpha (NAPA), point a complicated network of protein crosstalks that manipulate AC actions as well as might act in the form of innovative drug targets [104,110].

In Alzheimer's disease, changes in AC signaling apparently takes variable, nevertheless, equivalent deleterious directions. Plethora of studies have documented diminished AC actions decreased in Alzheimer's disease brains— maximum pronouncedly in the i) hippocampus as well as ii) cerebellum—in addition to that such diminishing is particularly noticeable in case of triggering AC is through Gs-coupled β-adrenergic receptors, in contrast to direct activation of the enzyme [111–113]. This points to a disturbance in the G-protein–AC coupling instead of in the catalytic working of AC itself. Noticeably, such dysfunction is not in view of the postmortem postponement or agonal factors nevertheless portrays disease particular change. Immunohistochemical studies have corroborated diminished expression of AC1 iii) as well as AC2 subtypes in pivotal brain region, inclusive of the i) hippocampus in addition to ii) neocortex [114].

The reduction which takes place in cAMP generation might result in dysfunctional PKA, along with CREB signaling, that are imperative for memory generation, along with synaptic plasticity [115,116]. Intriguingly, empirical studies have illustrated that AC hampering possesses the capability of triggering neurogenesis along with results in improvements in cognitive working in aged mice, yielding a paradoxical however plausibly therapeutic modality of considerable significance [117]. This points that precise modulation— instead of simple upregulation or downregulation—of AC action might provide cognitive advantages based the disease state as well as background.

The cAMP/PKA/CREB pathway is further involved in ALS. Cortical neurons obtained from an ALS patient's iPSCs illustrate diminished CREB activation, resulting in dysfunctional dendritic as well as synaptic health. Such dysfunctional activation associates with dendritic in addition to synaptic dysfunction, along with has been correlated with a disequilibrium in PKA subunit expression. significantly, manipulation of cAMP quantities has been illustrated to result s in rectification of CREB actions as well as improvement s in neuronal health [118]. The pathway is further implicated in controlling TAR DNA-binding protein 43 (TDP-43), a protein central to ALS pathology. TDP-43 accretion as well as cytoplasmic misplacement, both of which assist in neurodegeneration, are controlled by cAMP/PKA signaling [119]. In mouse models of ALS, activation of the cAMP/PKA pathway has been illustrated to revert synaptic deficiencies in spinal motoneurons, escalate their firing action, as well as result in improvements in working disease markers [120]. Additionally, an elimination of primary cilia in motor neurons—structures marked by the expression of AC3—has been determined in SOD1-G93A mice, pointing that the AC3 impairment in addition to disturbed cAMP signaling might assist in disease propagation [47]. Further embracing such, downregulation of cAMP/PKA/CREB signaling is escalatingly acknowledged in the form of a pathological characteristic in ALS. Pharmacological induction of such pathway utilizing agents for instance forskolin along with solanesol has shown neuroprotective activities, plausibly via escalation of mitochondrial working [121, rev by us in ref no 13]. Moreover, PACAP, a neuropeptide which activates adenylyl cyclase, has been demonstrated to facilitate motor neuron survival via s ed i) PKA-based transactivation of epidermal growth factor receptor (EGFR) in addition to ii) upregulation of pro-survival genes, inclusive of matrix metallopeptidase 2 (MMP-2) [122].

In SMA in addition to SBMA, escalating cAMP signaling has incepted in the form of an attractive working regarding protection conferring approach. In SMA, clinical robustness associates d inversely with the enrichment of totally spliced survival motor neuron (SMN) protein as well as with the plethora of SMN-positive nuclear "gems" [123]. Escalating intracellular cAMP—either by hampering \ phosphodiesterase-4 i) with rolipram or ii) by directly activating AC with forskolin—rectifies exon 7 inclusion in SMN2 transcripts in addition to escalates SMN protein, along with gem counts in patient- obtained fibroblasts, embracing cAMP up-regulation in the form of a therapeutic methodology [124,125]. A corresponding mechanistic mode operates in SBMA, a polyglutamine-expansion disease of the androgen receptor (AR). Activation of the AC/cAMP/PKA series lessens phosphorylation- based agglomeration of the mutant AR, diminishes its toxicity, and result in improvements in motor-neuron survival in cell along with mouse models [125,126].

## Pharmacological Mmanipulation of AC Activity

Pharmacological manipulation of adenylyl cyclase action has advented in the form of a robust approach in reference to escalating neuroregeneration as well as countering maladaptive plasticity.

- Small molecule activators for instance i) forskolin, ii) 8-bromo cAMP, in addition to iii) rolipram escalate intracellular cAMP along with therefore induce i) axonal growth, ii) synaptic remodeling, in addition to iii) working rectification in variable damage models [10,79].
- Rolipram, by hampering phosphodiesterase 4, i) elongates cAMP escalation as well as ii) offers analogous improvements in axon regrowth as well as iii) working results subsequent to spinal trauma [84,127,128].
- The membrane-permeant cAMP analog 8- bromo-cAMP simulates the actions of NGF, i) tackling myelin- correlated hampering to boost neurite extension [129]. The mechanistic mode that lies beneath implicates, i) activation of the MAPK/ERK along with ii) PI3K/Akt pathways

as well as, iii) inactivation of the Rho signaling pathway, total of which allow for cytoskeletal remodeling in addition to iv) escalated neurite outgrowth [130]. Transmembrane AC activators have exhibited important neuroprotective along with regenerative actions.

- Forskolin, a robust activator of transmembrane ACs, i) elevates cAMP quantities as well as has been illustrated to ii) aggravate axonal lengthening, iii) escalate remyelination, iv) in addition to rectify neuronal working in variable damage models [131].5.1cA In the PNS, forskolin mechanistic mode i)escalates peripheral nerve regeneration by diminishing the latency of axonal sprouting beginning as well as ii) causes improvements in Schwann cell working [130-132].
- In CNS conditions, forskolin has shown . therapeutic probability in 1)Parkinson's disease models i) by causing rectification of behavioral as well as ii) neurochemical deficiencies via i) activation of the AC/cAMP/PKA-CREB pathway in addition to, result in improvements in mitochondrial working [135,136]. Forskolin has further been demonstrated to facilitate i) remyelination, ii) rectify mitochondrial enzymes, along with) iii) lessens neuroinflammation in multiple sclerosis models [131].
- In Alzheimer's disease models, forskolin i) causes improvements in cognitive working, ii) lessens amyloid-β plaque accrual, in addition to iii) modulates inflammatory reactions [137].
- Furthermore, in dementia models, forskolin i) mitigates memory deficiencies, along with ii) demonstrates a) anticholinesterase, b) ant amyloid, c) antioxidative, as well as d) anti-inflammatory actions [138].

At the cellular magnitude, forskolin i) reverts amyloid-β-induced hampering of long-term heightening by escalating cAMP signaling [139]. Nevertheless, forskolin's actions on tau phosphorylation are complicated. Whereas it activates PKA in addition to escalates tau phosphorylation at plethora of regions correlated with Alzheimer's disease, this priming enables tau greater proneness to greater phosphorylation by glycogen synthase kinase-3 (GSK-3), pointing both greater advantageous along with plausibly inimical actions in Alzheimer's pathology [140,141].

Forskolin has further illustrated 5.1cB4) therapeutic advantages in Huntington's disease models, where it reverts behavioral deficiencies as well as rectifies biochemical frameworks in a dose- based fashion [142]. In a cell model of Huntington's disease that possesses the capability of getting induced, forskolin partly rectifies neurite outgrowth in addition to causes avoidance of cell death associated with polyglutamine enlargement by escalating CRE- modulated transcription [143]. Furthermore, forskolin rectifies motor working as well as avoidance of midbrain dopamine neuron elimination in a rat model of Parkinson's disease, illustrating ed superiority over canonical levodopa therapy in the form of a disease- manipulating therapeutic alternative [135].

In multiple sclerosis models, forskolin hampers inflammatory in addition to reactions, manipulate iron homeostasis, along with causes improvements in motor along with cognitive working by rectification of mitochondrial enzymesas well as neurotransmitter concentrations [131,144]. Moreover, forskolin has been assessed in the form of s i) a treatment for glaucoma, where it ii) diminishes intraocular pressure in addition to iii) induces neurotrophic factors, conferring protection to RGC's retinal ganglion cells from degeneration [145,146]. Clinical trials have illustrated forskolin's efficacy in diminishing intraocular pressure in open angle glaucoma patients, that enables it toact in the form of a plausible alternative to beta-blockers, specifically in patients with asthma [147]. Forskolin's neuroregenerative actions expand to spinal cord damage models, where on combining it with rosiglitazone escalates i) locomotor rectification, along with ii) neuronal healing [148]. iii) Additionally, i) forskolin synergizes with transforming growth factor beta 1 (TGF-β1) to reactivate chronically denervated Schwann cells, ii) causing improvements in axonal regeneration in damaged peripheral nerves. This combinational treatment meaningfully escalates the quantities of regenerated axons at the healing region as well as diminishes Schwann cell impairment correlated with chronic denervation [149,150]. Recently, attention has shifted to the distinct characteristics of soluble AC, that—separate from transmembrane isoforms—reacts directly to intracellular bicarbonate as well as calcium [12,151]. Pharmacological activation of sAC escalates RGC survival in addition to optic nerve regeneration, while its hampering curbs the neurotrophic actions of BDNF on myelin-hampered neurite outgrowth [55,57,152].

## PACAP

Pituitary adenylate cyclase-activating polypeptide (PACAP) is a considerably preserved neuropeptide which indirectly induces adenylyl cyclase via activation of Gs-coupled receptors (Gs-GPCRs). It is broadly expressed all through the CNS, inclusive of critical sites for instance the i) hippocampus, ii) cortex, as well as iii) hypothalamus [153]. Amongst the plethora of Gs-GPCR agonists possess the capability of escalating intracellular cAMP quantities, PACAP is discriminated by its extraordinary robustness in addition to wide spectrum of its neuroprotective, along with neuroregenerative actions. PACAP escalates i) neuronal survival as well as ii) axonal regeneration by activating AC in addition to, iii) that gets followed by the PKA/CREB transcriptional axis getting engaged. Additionally, it modulates plethora of key cellular events germane to nervous system damage along with neurodegeneration for instance i) neuroinflammation, ii) calcium signaling, as well as iii) mitochondrial function [154,155]. Further than he PKA pathway, PACAP-initiated cAMP signaling further activates series for instance MAPK in addition to phospholipase C (PLC) pathways, which are key for i) cell survival, ii) differentiation, along with iii) axonal growth [156,157]. Such actions are modulated through three G-protein-coupled receptors— i) pituitary adenylate cyclase-activating polypeptide type I receptor (PAC1), ii) vasoactive intestinal peptide receptor 1 (VPAC1), as well as iii) vasoactive intestinal peptide receptor 2 (VPAC2)— every one possesses unique signaling characteristics. Whereas PAC1 as well as VPAC1 receptors are coupled with AC, resulting in cAMP generation, they further engage PLC to induceCa2+ mobilization in addition to PKC activation, affecting cellular reactions for instance growth, along with survival [158-161]. The activation of such pathways by PACAP is tissue-as well as production -stage-particular, i) ii) iii) pointing the complicated nature of its part in both normal physiology in addition to neuroregenerative events [162,163] (Figure 4). Taken together, such credits make PACAP apart from an archetypal but further possesses extraordinary properties of well-studied instance of indirect AC activation with greater translational germaneness for neuroregenerative approaches.

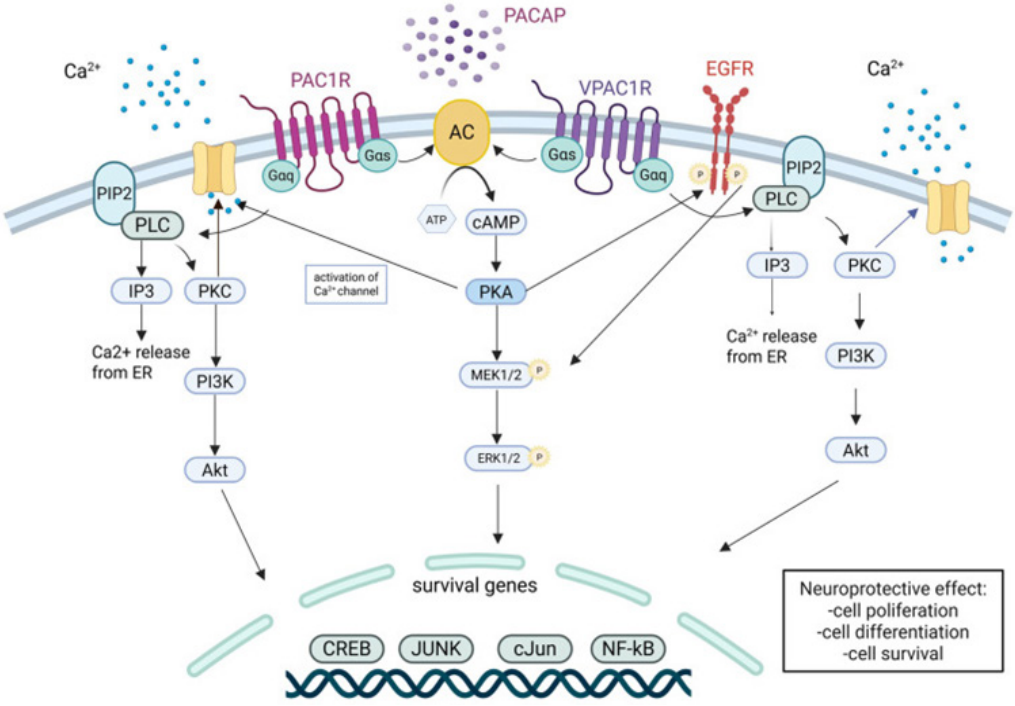


**Figure 4:** Courtesy ref no-9--Pituitary Adenylate Cyclase-Activating Polypeptide (PACAP) receptor-mediated signaling pathways promoting neuroprotection. PACAP exerts neuroprotective effects through activation of its high-affinity receptor PAC1R (PACAP type I receptor) and low-affinity receptors: VPAC1R (vasoactive intestinal peptide receptor 1) and VPAC2R (vasoactive intestinal peptide receptor 2), which are coupled with G-proteins (Gαs and Gαq). Upon PACAP binding, these receptors activate adenylyl cyclase (AC), leading to cyclic adenosine monophosphate (cAMP) production and protein kinase A (PKA) activation. PKA phosphorylates downstream targets including MEK1/2 (mitogen-activated protein kinase kinase 1/2) and ERK1/2

(extracellular signal-regulated kinase 1/2), which translocate to the nucleus to regulate transcription of survival genes such as CREB (cAMP- response element-binding protein), JUN, cJUN (jun proto-oncogene), and NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells). In parallel, PACAP receptors also engage the PLC/IP3/PKC signaling cascade via Gαq. This includes phospholipase C (PLC) activation, generation of inositol 1,4,5-trisphosphate (IP3), and stimulation of protein kinase C (PKC), leading to calcium (Ca2+) release from the endoplasmic reticulum (ER). This calcium signaling supports activation of the phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) pathway, which is crucial for cell survival and growth. Additionally, epidermal growth factor receptor (EGFR) transactivation may amplify PLC-dependent signaling. Collectively, these pathways contribute to PACAP's neuroprotective functions, including cell proliferation, differentiation, and resistance to apoptosis. Created in BioRender. Tomczak, J. (2025) https://BioRender.com/mt2mtgo.

In the case of peripheral nervous system (PNS), PACAP possesses imperative part in facilitating axonal regeneration subsequent to damage. When peripheral nerves are damaged, PACAP quantities escalate in the distal nerve stump in addition to DRG neurons, that promotes axonal outgrowth along with regeneration [164,165]. Such modulated regenerative action s is modulated by PACAP's capacity of inducing Schwann cells, that are pivotal for the healing as well as remyelination of injured axons. PACAP escalates the expression of myelin- associated genes in Schwann cells in addition to controls the inflammatory reaction s in the damaged nerve aiding in, both remyelination along with the rectification of inflammation [166,167]. Single-cell RNA sequencing of DRG neurons documented Adcyap1 factor in the form of a protection conferring that associated pain as well as nerve regeneration subsequent to damage. Intrathecal delivery of PACAP38, the protein encoded by Adcyap1, attenuated pain in addition to facilitated axonal regeneration in a rat model of spared nerve crush [165]. Such activities emphasize PACAP's imperative part in post- damage rectification, along with nerve regeneration. Moreover, PACAP's capability of manipulating inflammation in the damaged peripheral nerve reinforces further its significance in facilitating a regenerative milieu, due to it hampers the liberation of pro-inflammatory cytokines in addition to escalates the expression of anti-inflammatory cytokines, that is pivotal for tissue healing along with regeneration [167,168].

In the case of central nervous system (CNS), PACAP exerts potent neuroprotective actions which are vital in a range of neurological disorders, inclusive of i) stroke, ii) neurodegenerative diseases (NDD), as well as iii) traumatic brain damages. The neuroprotective actions of PACAP are mainly accredited to its activation of PAC1 receptors, that start a cascade of intracellular processes with the objective of conserving neuronal wholeness. These are inclusive of the i) controlling of ionic homeostasis, ii) diminishing in excitotoxicity, in addition to iii) hampering of oxidative stress, all of which allow for avoidance of neuronal demise in the face of damage [157,169]. For example, PACAP has been illustrated to confer protection to neurons from ischemic damage in models of stroke by i) manipulating NMDA receptor subunits, along with ii) diminishing calcium over burden, a main cause of cell demise subsequent to ischemic processes [170]. In PD, PACAP possesses a neuroprotective part by causing avoidance of the degeneration of dopaminergic neurons as well as escalating their survival in both in vitro in addition to in vivo models [155,171]. PACAP has further been involved in manipulating autophagy in PD, diminishing autophagic action, along with conferred protection to neurons from the toxic actions of proteins accrual, a landmark of PD pathology [172, 173]. Such observations embrace PACAP's probability in the form of a therapeutic agent in treating NDD, where neuronal demise as well as impairment are frequent. PACAP's neuroprotective actions extend to other neurodegenerative disorders for instance Alzheimer's disease and Huntington's disease, where it has been illustrated to attenuate cognitive reducing along with conferred protection to synaptic working [155,174]. In AD models, PACAP allow for avoidance of the neurotoxic actions of amyloid-beta plaques, that helps in neuronal impairment in addition to elimination. Via its effect on the PAC1 receptor, PACAP facilitates the liberation of neurotrophic factors for instance BDNF, that is imperative for synaptic plasticity along with cognitive working, further embracing its therapeutic plausibility in such diseases [175]. Apart from its neuroprotective characteristics, PACAP is implicated in manipulating inflammation as well as apoptosis, both of which possess significant parts in the propagation of NDD. By diminishing neuroinflammation along with hampering

apoptotic pathways, PACAP accounts for sustenance of neuronal survival in addition to working in chronic diseases[176, 177].

Although it possesses attractive therapeutic actions, the clinical application of PACAP is hampered by obstacles, specifically its swift in vivo breakdown as well as the peripheral inimical sequelae accompanied by VPAC1 as well as VPAC2 receptor activation, that possesses the capability of resulting in undesired vasodilation in addition to escalated heart rate [177]. In order to overcome such concerns, researchers have generated PACAP analogs with improvement of stability, along with selectivity for the PAC1 receptor. Manipulated peptides for instance [Ala (7)] PACAP27 in addition to [Hyp (2)] PACAP27 have illustrated escalated resistance to breakdown as well as escalated neuroprotective actions, specifically in models of PD in addition to ischemic stroke [178. An extra issue for PACAP- dependent therapies is its restricted capacity of crossing the blood brain barrier (BBB). In reference to tackling botherations, alternative administration approaches for instance serves i) intranasal delivery, along with ii) nanoparticle- dependent drug delivery systems are getting assessed, with the objective of PACAP quantities in the brain whereas try to ensure a minimal of systemic exposure [175]. Such strategies possess es the capability of importantly escalating PACAP's clinical viability, allowing efficacious therapies s of disorders for instance i) stroke, ii) AD, iii) PD, along with iv) multiple sclerosis [179]. Additionally, recent studies have emphasized s PACAP's role in neurogeneration. PACAP promotes neurogenesis in the adult brain, specifically in the hippocampus, which is crucial critical for learning as well as memory [180]. Via its effect on PAC1 receptors, PACAP increase the survival of newly generated neurons, embracing cognitive working in addition to rectification subsequent to brain damage [181,182]. Moreover, PACAP is involved in the controlling of synaptic plasticity, imperative for i)) learning, ii) memory, along with iii cognitive working, pointing that it embraces apart from conferring protection to neurons however further the development of newer neurons [183,184]. In the backdrop of traumatic damages, PACAP possesses a vital part in tissue healing as well as regeneration, specifically in spinal cord well as traumatic brain damage models [185,186]. Subsequent to damage, PACAP quantities escalate in the damaged tissue, where they facilitate neuronal survival as well as axonal regeneration, promoting working rectification. The peptide's capability of manipulating inflammation in addition to facilitate tissue healing further reinforces its plausibility in the form of a therapeutic target for both traumatic, along withl ischemic brain damages [154,186-188].

### *AC Hampering Agents*

Adenylyl cyclase hampering agents have recently garnered interest in the form of plausibile therapeutic agents for NDD in view of their capacity of manipulating intracellular signaling pathways that control i) neurogenesis, ii) neuronal survival, in addition to iii) neural healing. Hampering of AC has been demonstrated to possess meaningfull actions on the CNS, specifically in facilitating neuroregeneration [189]. Recent studies have shown that AC hampering possesses the capability of escalating neural stem cell (NSC) proliferation along with neural progenitor cell (NCP) actions, specifically in sites implicated in neurogenesis for instance the subventricular zone (SVZ). In a mouse model of Alzheimer's disease, the delivery of 2′ ,5′ -Dideoxyadenosine, an AC hampering agent, caused a meaningfull escalation in NSC as well as NCP populations, that correlated with improvements in age- correlated cognitive in addition to behavioral deficiencies. Such improvements were inclusive of i)) escalated exploratory behaviour , along with ii) better conduction in conditioned reflex investigations, pointing that AC hampering possesses the capability of resolution of a minimal of certain angles of neurogenesis that are reduced in neurodegenerative disorders. Such escalation in neurogenic capability of correlated escalated neuroglial embracing, due to oligodendrocytes as well as microglia were induced to cause liberation of neurotrophic growth factors, further facilitating brain healing [117]. The advantages of AC hampering protracted further than Alzheimer's disease. In a model of ethanol stimulated neurodegeneration, chronic ethanol exposure led to meaningfull neuropsychiatric impairments, inclusive of i) neuronal degeneration, ii) escalated motor actions, in addition to iii) cognitive dysfunction. Histological evaluation documented considerable injury in the brain, inclusive of i) edema, ii) perivascular inflammation, along with iii) excitotoxicity. Delivery of AC hampering agents caused considerable neuroprotection, with a diminishing in neuronal degeneration in addition to rectification of NSC, along with NCP proliferation.Such working

rectification was credited to the manipulation of cAMP signaling, which i) escalated neuroregenerative events as well as ii) embraced glial cell working. AC hampering caused rectification of the orchestration amongst NSC proliferation in addition to NCP activity, a vital factor for brain regeneration [190].

The probability of AC hampering agents in tackling synaptic impairments as well as excitotoxicity arises primarily from studies of the calcium-sensitive isoform AC1. In case of physiological situations, AC1 gets activated by Ca2+/calmodulin in addition to embraces synaptic buttressing, along with memory generation. Nevertheless, once NMDA receptors are overinduced, escalated AC1 actions possesses the capability of aggravating alcium overburden as well as guide excitotoxic neuronal demise [191]. Genetic elimination or pharmacological hampering of AC1 has been illustrated to confer protection to neurons from glutamate- in addition to NMDA stimulated-toxicity: cortical cultures from AC1 knockout mice maintain lesser excitotoxic demise, along with in vivo NMDA- disfigurement models once in case of lack of AC1 is present develop smaller cortical damages. Moreover, AC1 knockout animals document flattening inflammatory reactions, further reinforcing AC1′ s central part in maladaptive plasticity [191-193]. In view of excitotoxicity—guided by excessive glutamate in addition to decontrolled calcium—is a final common pathway in plethora of neurodegenerative conditions, targeting AC1 yields an attractive commensurate to existing NMDA-modulating drugs for instance memantine, whose advantages continues to be modest [194]. Additionally, research points that AC hampering agents possess the capacity of manipulating the complicated nature of cAMP/PKA signaling pathway, that control variable facets of neurogenesis as well as glial cell actions. In physiological, cAMP signaling facilitates NSC proliferation whereas hampering NCP mitotic actions. Nevertheless, in pathological states for instance ethanol stimulated neurodegeneration, such orchestration is disturbed, causing dysfunctional neurogenesis, along with the brain's capability of healing itself. Hampering of AC in models rectification of the appropriate working of NSCs as well as NCPs, facilitating neurogenesis in addition to escalating glial advocate mechanistic modes [190]. Apart from their neuroregenerative characteristics, AC hampering agents have illustrated attraction in the therapy of chronic pain.

AC1 has been isolated in the form of a crucial actor in neuropathic pain, with studies illustrating that selective hampering of AC1 possesses the capability of diminished pain correlated - cortical heightening, along with mechanical hypersensitivity in animal models of chronic pain. Separate from canonical pain therapies, that usually have meaningfull inimical sequelae, AC1 hampering agents do not cause dysfunctional cognitive or motor working, that enables them an attractive non-opioid alternative for pain management [195,196]. Screening attempts have isolated innovative AC1-selective hampering agent scaffolds with plausibility for further generation [197]. In vitro cellular models have been generated to evaluate AC1 hampering agents' actions on pain- associated signaling pathways [198]. Noticeably, the selective AC1 hampering agent ST034307 has illustrated efficaciousness in yielding pain relief in variable kinds in mouse models without resulting in analgesic tolerance subsequentto chronic dosing [199].

## Conclusions along with Future Directions

Adenylyl cyclases are vital governers of cAMP signaling, that manipulates plethora of events in the nervous system. Considerable proof from empirical models illustrates that AC- developed cAMP facilitates transcription of i) pro-regenerative genes, ii) cytoskeletal remodeling as well as iii) neuronal-glial crosstalks that are imperative for working rectification subsequent to neural damage [55,79]. Amongst the ten mammalian AC isoforms, AC1, AC8, AC5, in addition to sAC are specifically germane to neuroregeneration owing to their unique controlling mechanistic modes, along with organization. AC1 as well as AC8, both calcium/calmodulin-sensitive, i) couple neuronal actions to cAMP generation in addition to ii) assist in synaptic plasticity, ii) axon outgrowth, along with iii) cognitive working, despite AC1 further possesses a maladaptive part in chronic pain [200,201]. AC5, expressed basically in the basal ganglia along with striatum, is implicated in dopaminergic signaling as well as has been involved in motor control as well as PD pathophysiology [202,203].

Compared to, sAC, which reacts with i) intracellular bicarbonate as well as calcium, ii) serves in the form of a metabolic sensor in addition to iii) facilitates axonal regeneration in hampering CNS milieu. i) It embraces neurite outgrowth by incorporating ionic signals with gene transcription ii) in reactions to factors for

instance BDNF [22,60]. In reference to a therapeutic viewpoint, both activations along with hampering of ACs have illustrated clinical plausibility, i) on the basis of isoform as well as ii) kinds of disease [208]. Pharmacological activation utilizing compounds for instance i) forskolin, ii) PACAP, as well as iii) PDE4 hampering agents has escalated axonal regrowth in addition to neuroprotection in models of spinal cord damage, PD, along with multiple sclerosis [148,171,204]. On the other hand, selective hampering of AC1 utilizing compounds for instance NB001 or ST034307 has efficaciously diminished maladaptive synaptic potentiation in addition to neuropathic pain without causing dysfunction of normal synaptic working [195,205]. Although such advancements have taken place, plethora of botherations hindered clinical translation, that are inclusive of the non-selective nature of present manipulating compounds, the BBB's restricted permeability, along with remunerating mechanistic modes amongstAC isoforms. Future attempts need to concentrate on the generation of isoform-selective AC manipulating compounds with attractive pharmacokinetic characteristics as well as CNS penetrance [189, 206]. Combination treatments incorporating AC-targeted compounds with neurotrophic factors or anti-inflammatory agents might further escalate their therapeutic plausibility, specifically in chronic or disorders that have plethora of etiological factors. Novel administration systems, for instance i) intranasal delivery in addition to ii) nanoparticle- dependent carriers, possesses the capability of meaningfully causing improvementof drug accessiblity to the brain as well as spinal cord [207–209].

Recent studies have utilized advancements regarding molecular profiling methodologies, for instance i) spatial, along with ii) single-cell transcriptomics, to assess the properties of cellular reactions at the time of damage as well as regeneration. Such strategies yield greater -resolution understanding into the i) multifaceted nature in addition to ii) dynamics of cell populations amongst the nervous system [210–212]. It is predicted that the incorporation of single-cell transcriptomics with spatial proteomics might be capable of mapping the i) cell- kinds - along with ii) backdrop particular expression designs of AC isoforms over variable stages of neural damage as well as healing. Such acknowledgement would be imperative for the germane generation of isoform-particular in addition to individualized therapeutic approaches targeting ACs in neuroregenerative medicine. Furthermore, the parts of ACs protract further than neurons to surround on-neuronal cells for instance i) Schwann cells, ii) astrocytes, along with iii) microglia, that are vital modulators of i) inflammation, ii) trophic embracing, as well as iii) tissue remodeling. A.In Schwann cells, cAMP quantities diminish meaningfully, controlled by AC activity, are intricately regulated at the time of demyelination as well as remyelination events. Subsequent to peripheral nerve damage, cAMP quantities diminish importantly, associating with diminished AC activity, in addition to just at the time of remyelination, emphasizing the significance of ACs in peripheral nerve regeneration [79].

B.In astrocytes, ACs possess a pivotal part in manipulating inflammatory reactions as well as neuroprotection. For example, activation of ACs in astrocytes results in escalated cAMP generation, affecting the liberation of neurotrophic factors in addition to cytokines, therefore influencing neuronal survival, along with inflammation [213,214].

C)Microglia, the resident immune cells of the CNS, further express ACs that modulate their activation states.Escalated cAMP quantities in microglia, that result in view of AC activation, have been correlated with a switching towards an anti-inflammatory phenotype, diminishing the generation of pro-inflammatory cytokines as well as facilitating tissue healing [215,216]. Such observations point to that AC signaling in glial cells possess the capacity of meaningfully affecting regenerative results outcomes. Getting insights regarding the ACs manipulate the working of such embracing cells possesses the capability of opening innovative vistas for therapeutic arbitration which overtakes neuron-centric approaches. In summary, adenylyl cyclases a versatile in addition to attractive class of targets in regenerative neuroscience. Their isoform- particular parts in regulating neuroplasticity, damage reaction, along with pathological remodeling provide plethora of options in reference to taking therapeutic advantages. Persistent evaluation of the molecular specificity, physiological germaneness, as well as pharmacological manipulation of AC isoforms would be vital regarding advancements of therapies regarding neurological damages in addition to NDD.

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