In the central nervous system (CNS), cyclic adenosine monophosphate (cAMP) plays a critical role in numerous, often concurrent, neuronal functions including survival, growth, differentiation and synaptogenesis. Elucidating the mechanisms by which this ubiquitous secondary messenger influences these processes is crucial to understanding why CNS neurons fail to regenerate after injury or in disease. Several survival and growth promoting pathways have been linked to cAMP signaling in neurons, including mitogen-activated protein kinase (MAPK), phosphatase and tensin homolog (PTEN), and signal transducer and activator of transcription 3 (STAT3), however, the molecular mechanisms by which cAMP specifically influences these pathways is still unclear. Recent evidence suggests that the context, extent and means by which cAMP signaling takes place account for its ability to simultaneously regulate survival and growth within neurons (Corredor et al., 2012; Wang and Cameron et al., 2015; Averaimo et al., 2016). These findings raise further questions about how cAMP signaling and survival signaling itself change after injury or in disease, and to what degree the intracellular compartmentation of cAMP signals is critical for its function in regulating neuroprotection and regeneration (Cameron and Goldberg, 2016).

In mammals, cAMP is synthesized by a family of nine transmembrane adenyl cyclases (tmACs, AC1-9) and one bicarbonate-and calcium-sensitive soluble adenyl cyclase (sAC, AC10). Neurons express six tmACs, as well as sAC, and thus likely employ multiple cAMP signaling mechanisms to regulate survival and growth. In retinal ganglion cell (RGC) neurons, electrical activity potentiates neurotrophic responsiveness in a cAMP-dependent manner, presumably through the increase of intracellular calcium. Interestingly, pharmacological inhibition and gene deletion of calcium-sensitive tmACs have no effect on baseline RGC survival or growth (Corredor et al., 2012). Conversely, inhibiting sAC signaling decreases RGC growth, and sAC gene knockout (KO) severely perturbs normal RGC and photoreceptor differentiation (Shaw et al., 2016). Thus, it appears that sAC, and not tmACs, is the major source of cAMP that drives survival and growth signaling in CNS neurons. Still, these findings only partially explain how sAC-derived cAMP may influence these processes, as sAC is expressed in multiple subcellular compartments including the nucleus, mitochondria and cytoplasm (Corredor et al., 2012). Further still, cAMP activates three distinct effectors, protein kinase A (PKA), exchange protein directly activated by cAMP (EPACs) and cyclic nucleotide-gated channels (CNGc), which themselves can differentially influence numerous downstream signaling pathways. How then does sAC-derived cAMP precisely modulate survival and growth in CNS neurons?

A general hypothesis is that cAMP specificity is achieved through compartmentalized cAMP signaling. cAMP synthesis, cAMP dynamics are modulated by phosphodiesterases (PDEs), a large, diverse family of enzymes that degrade cyclic nucleotides and control their concentration, localization and lifetime. PDE activity has been linked to neuronal survival, growth and synapse formation. For example, Rolipram, a selective PDE4 inhibitor, reportedly promotes neuroprotection and perturbs axon dieback following acute spinal cord injury (Schaal et al., 2012). Further, synaptic plasticity and memory can be impaired by expression of a full length PDE4A5 isoform in hippocampal neurons that associates with dendritic compartments but not a PDE4A5 truncation mutant (lacking an N-terminal targeting domain) that localizes exclusively in the perinuclear space (Havekes et al., 2016). Together, these data support the hypothesis that subcellular localization and strict control of cAMP levels by sAC and PDEs impart the specificity required to regulate growth, survival and synaptogenesis in CNS neurons. But what dictates where sAC-derived cAMP signaling takes place within a neuron?

Spatial-temporal control of cAMP signaling is often conferred by a heterogeneous family of multivalent scaffold proteins called A-kinase anchoring proteins (AKAP), so-called due to their binding of the cAMP effector PKA. AKAPs are expressed in every cell type, but have been especially well-characterized in cardiac myocytes and neurons where they facilitate localized signaling within distinct microdomains through the organization of signalosomes containing specific isoforms of ACs, PDEs and PKAs. In addition, AKAPs enable crosstalk between the cAMP pathway and known regulators of neuronal growth and survival such as extracellular signal-regulated kinases (ERKs) and calcium-regulated nuclear factor of activated T-cells (NFAT) transduction.
Neural regeneration research is focused on understanding and manipulating the natural regenerative abilities of the nervous system. The activity of cyclic nucleotide signaling in injured retinal ganglion cells (RGCs) is particularly relevant in the context of promoting CNS repair and regeneration. In this study, we investigate the role of cyclic AMP (cAMP) signaling in the promotion of RGC axon regeneration after injury.

**References**


