Cellular Signalling 42 (2018) 281–291

Contents lists available at ScienceDirect

Cellular Signalling

journal homepage: www.elsevier.com/locate/cellsig

Review

Cyclic nucleotide signaling changes associated with normal aging and age-related diseases of the brain

Michy P. Kelly

Department of Pharmacology, Physiology & Neuroscience, University of South Carolina School of Medicine, 6439 Garners Ferry Road, VA Bldg 1, 3rd Floor, D-12, Columbia, SC 29209, United States

ARTICLE INFO

Keywords:
Aging
Age-related cognitive decline
Mild cognitive impairment
Cyclic nucleotides
cAMP
cGMP
Phosphodiesterase
Memory
Alzheimer's disease
Huntington's disease
Parkinson's Disease
Hippocampus
Cortex
Striatum
Cerebellum
PDE1
PDE3
PDE7
PDE8
PDE11

ABSTRACT

Deficits in brain function that are associated with aging and age-related diseases benefit very little from currently available therapies, suggesting a better understanding of the underlying molecular mechanisms is needed to develop improved drugs. Here, we review the literature to test the hypothesis that a break down in cyclic nucleotide signaling at the level of synthesis, execution, and/or degradation may contribute to these deficits. A number of findings have been reported in both the human and animal model literature that point to brain region-specific changes in Galphas (a.k.a. Gαs or Gsα), adenylyl cyclase, 3′,5′-adenosine monophosphate (cAMP) levels, protein kinase A (PKA), cAMP response element binding protein (CREB), exchange protein activated by cAMP (Epac), hyperpolarization-activated cyclic nucleotide-gated ion channels (HCNs), atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), soluble and particulate guanylyl cyclase, 3′,5′-guanosine monophosphate (cGMP), protein kinase G (PKG) and phosphodiesterases (PDEs). Among the most reproducible findings are 1) elevated circulating ANP and BNP levels being associated with cognitive dysfunction or dementia independent of cardiovascular effects, 2) reduced basal and/or NMDA-stimulated cGMP levels in brain with aging or Alzheimer's disease (AD), 3) reduced adenylyl cyclase activity in hippocampus and specific cortical regions with aging or AD, 4) reduced expression/activity of PKA in temporal cortex and hippocampus with AD, 5) reduced phosphorylation of CREB in hippocampus with aging or AD, 6) reduced expression/activity of the PDE4 family in brain with aging, 7) reduced expression of PDE10A in the striatum with Huntington's disease (HD) or Parkinson's disease, and 8) beneficial effects of select PDE inhibitors, particularly PDE10 inhibitors in HD models and PDE4 and PDE5 inhibitors in aging and AD models. Although these findings generally point to a reduction in cyclic nucleotide signaling being associated with aging and age-related diseases, there are exceptions. In particular, there is evidence for increased cAMP signaling specifically in aged prefrontal cortex, AD cerebral vessels, and PD hippocampus. Thus, if cyclic nucleotide signaling is going to be targeted effectively for therapeutic gain, it will have to be manipulated in a brain region-specific manner.

1. Introduction

3′,5′-cyclic nucleotides (cAMP and cGMP) are intracellular signaling molecules that regulate a myriad of processes in the central nervous system (CNS), including neurogenesis, the establishment of neuronal circuitry, apoptosis, plasticity, sleep, sensorimotor gating, mood stability, memory and other cognitive functions [1–12]. Aging and age-related diseases, including Alzheimer's disease, Huntington's disease (HD), and Parkinson's disease (PD), are associated with impairments in many, if not all, of these processes (e.g., [13–16]), suggesting cyclic nucleotide signaling may be compromised in these patient populations.

Both the cAMP and cGMP pathways are composed of numerous molecules responsible for the synthesis, execution, and breakdown of their signals (Fig. 1). It has long been known that cAMP is synthesized in the brain by transmembrane adenylyl cyclases (ACs), which are activated by Gαs and inhibited by Gαi [17]. More recently, however, it was shown that cAMP is also synthesized in the brain by soluble ACs, which are expressed in mammalian glia and neurons and are activated by bicarbonate and calcium [18]. cGMP is synthesized by particulate guanylyl cyclases (pGCs), which are activated by natriuretic peptides, and soluble guanylyl cyclases (sGCs), which are activated by nitric oxide (NO) [19]. cAMP activates protein kinase A (PKA), exchange protein activated by cAMP (Epac), and cyclic nucleotide gated channels; whereas, cGMP activates protein kinase G (PKG) and cyclic nucleotide gated channels. Activation of either the cAMP or cGMP pathways can ultimately lead to activation (i.e., phosphorylation) of cAMP response element binding protein (CREB) to facilitate transcription of CRE-dependent genes. cAMP and cGMP are degraded by 11 families of

E-mail address: Michy.Kelly@uscmed.sc.edu.

https://doi.org/10.1016/j.cellsig.2017.11.004
Received 16 October 2017; Accepted 21 November 2017
Available online 23 November 2017

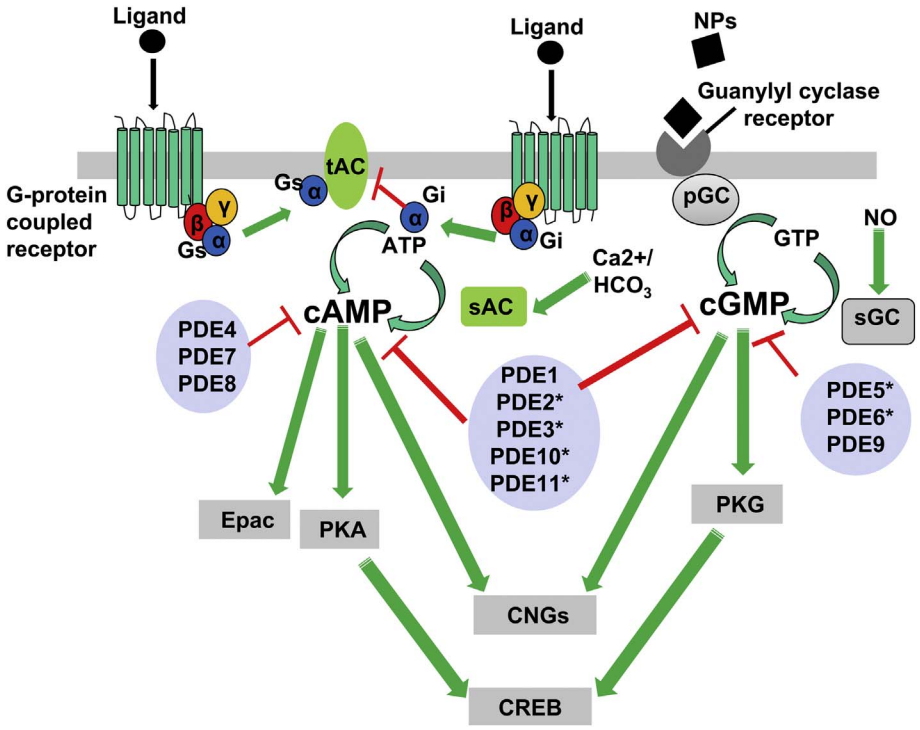

Fig. 1. Signaling cascades responsible for the synthesis, execution, and break down of cAMP and cGMP signals. G-protein coupled receptors activate heterotrimeric G-proteins containing either an inhibitory (Gi) or stimulatory (Gs) alpha subunit (by facilitating displacement of a bound GDP for GTP) that acts on transmembrane adenylyl cyclase (tAC). In contrast, calcium and bicarbonate (HCO3) activate soluble AC (sAC). ACs synthesize the formation of 3′,5′-cyclic adenosine monophosphate (cAMP) from ATP. cAMP can then activate exchange protein activated by cAMP (Epac), protein kinase A (PKA), or cyclic nucleotide gated channels (CNGs). Natriuretic peptides (NPs) activate particulate guanylyl cyclase (pGC)-coupled receptors, and nitric oxide (NO) stimulates soluble GC (sGC). GCs synthesize the formation of 3′,5′-cyclic guanosine monophosphate (cGMP) from GTP. cGMP activates protein kinase G (PKG) and CNGs. Activation of PKA and/or PKG leads to phosphorylation and activation of the transcription factor cAMP response element binding protein (CREB). 11 families of 3′,5′-cyclic nucleotide phosphodiesterases (PDEs) hydrolyze cAMP and/or cGMP, and the activity of select PDEs (indicated by*) is allosterically regulated by cAMP or cGMP.

phosphodiesterases (PDEs), some of which are allosterically modulated by cAMP and cGMP themselves [20]. Here we review the literature to test the hypothesis that dysfunction in the synthesis, execution, and/or degradation of cAMP/cGMP signals occurs in the central nervous system and/or circulation with aging and age-related diseases.

2. Alterations in cyclic nucleotide signaling associated with aging

Studies show mixed results regarding the effect of age on cAMP synthesis. Reductions in basal and Gαs-stimulated AC activity were correlated with increasing age in human brain samples (region not specified, [21]). Unfortunately, animal studies are highly conflicted with regard to reports of age-related changes in AC activity. In any given brain region (hippocampus, cortex, striatum and cerebellum), approximately half of animal studies showed age-related reductions in AC activity and the other half of studies showed no age-related change in AC activity [22–28].

Reports of age-related changes in cAMP levels in human tissue are sparse and those in rodent brain are somewhat conflicting, but some general trends emerge (Fig. 2B). In humans and rodents, basal cAMP levels were decreased in aged vs. young adult white blood cells [29–32]. cAMP levels were also reduced in serum from aged vs. young adult rodents [33], but remained unchanged in aged human cerebral microvessels [34,35]. Basal cAMP levels do not appear to change with age in the rodent hippocampus [22,25,36,37]; however, traumatic brain injury (TBI) reduces hippocampal cAMP levels significantly more in aged vs. young adult rodent hippocampus [36]. Similarly, basal cAMP levels do not appear to differ between aged and young adults in the rodent cerebellum [22,25] (but see [38]); however, norepinephrine- and kainite-stimulated cAMP levels do appear to be significantly diminished in cerebellum of aged rodents [37]. In contrast, basal cAMP levels are decreased in aged rodent cortex [22,25,39,40] (but see [36,37]), as are basal cAMP levels in thalamus and/or hypothalamus [25,36] (but see [37]). In this light, it is then striking that infusion of a cAMP analogue specifically into prefrontal cortex actually mimics—instead of rescues—age-related deficits in working memory; whereas, infusion of a cAMP blocker reverses age-related deficits in working memory and corresponding neurophysiological endpoints [41–43]. This ability of a cAMP blocker to reverse working memory deficits is particularly difficult to reconcile with the fact that PKA activity is also significantly decreased in prefrontal cortex of aged vs young adult rodents [44], as it is in rodent hippocampus [44,45], rodent serum [33], and fly brain [46]. PKA activity is not always reduced with aging, however, as increased PKA activity was noted in cerebral microvessels from aged vs. young adult rodents [47]. Thus, the effect of aging on cAMP signaling appears to be brain region specific.

The effects of age on cAMP-PDE expression and/or activity are widely variable, depending on the specific isoform and tissue (Table 1). No change was seen in cAMP-PDE activity in aged rat serum [33], but high Km cAMP-PDE activity was found to be increased in cortex and hippocampus of aged vs. young adult rodents [48,49]. The isoform(s) responsible for the increased cortical cAMP-PDE activity is unclear given that both PDE4 and PDE7A expression and/or activity appear to be downregulated in cortex and PDE8 shows no change [50–53] (Table 1). Given that PDE7A mRNA was reduced in aged rat cortex, it is interesting to note that a PDE7A single nucleotide polymorphism (SNP) was genetically linked to age-related cognitive decline in 3 replication cohorts and a joint analysis [54]. Decreases in PDE4 expression and activity have also been noted in striatum and cortex of both rat and monkey [50–53], including in dorsolateral prefrontal cortex [51]. The latter data are consistent with findings that the PDE4 inhibitor rolipram impairs working memory in monkeys in a manner that correlates with advancing age [41], but are difficult to reconcile with the suggestion that a PDE4 inhibitor improves working memory in elderly humans (see [55]). Decreases in PDE4 expression and activity have also been reported in cerebellum of rat [53,56], but were not replicated in monkey [57]. In contrast, an increase in PDE4 activity was reported in the basal forebrain of aged vs. young adult rats [58]. Although PDE4 protein expression decreases in hippocampus [56,57] (but see [53]), PDE1C, PDE8A, and PDE11A expression increased in aged vs. young adult rodent hippocampus [50]. These increases in PDE1C, PDE8A, and PDE11A may account for the age-related increases in high Km cAMP-PDE activity that were described above [48] as well as age-related increases in hippocampal cGMP-PDE activity that have been reported [49]. These region-specific changes in PDE expression/activity suggest it will be important to target this signaling cascade in a region-specific