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

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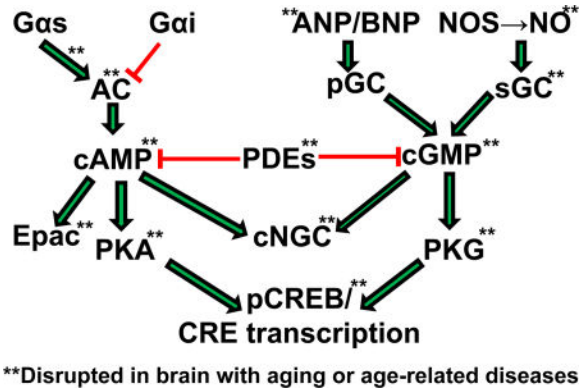
Abstract

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 nucleotidegated 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.

Graphical abstract



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; PDE2; PDE3; PDE4; PDE5; PDE7; PDE8; PDE9; PDE10; PDE11; cyclase; natriuretic peptide

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 (Figure 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 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 (Figure 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]); but, norepinephrine- and kainite-stimulated cAMP levels appear to be significantly diminished in cerebellum of aged rodents [37]. In contrast, basal cAMP levels do appear to decrease in aged rodent cortex [22,25,39,40] (but see [36,37]), as do 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 levels 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). 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). 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 manner in order to obtain efficacy with minimal side effects.

Consistent with a role for upregulated cAMP-PDE activity in the pathophysiology of age-related cognitive decline, a number of cAMP-PDE inhibitors have demonstrated therapeutic effects in both preclinical and clinical studies. In addition to antagonizing adenosine receptors, caffeine is known to inhibit PDEs, particularly cAMP-PDE activity [59]. In elderly women, higher caffeine consumption reduced the risk of developing cognitive impairment [60] and slowed the rate of cognitive decline [61]. Studies in rodents similarly show that chronic caffeine can prevent the onset of age-related cognitive decline [62–64] (but see [65]). PDE inhibitors targeting specific cAMP- or dual-specific PDEs have also shown pro-cognitive effects in aging. A drug containing the PDE1 inhibitor vinpocetine improved memory function in elderly subjects [66], as have 2 novel PDE4 inhibitors from Dart Neuroscience and Tetra Discovery Partners (see [55]). In animal models, pharmacological inhibition or genetic deletion of PDE2 [67], PDE3 [68], PDE4 [69–72], and PDE8B [73] have all provided protection against some type of age-related cognitive decline. These studies suggest that increasing cAMP signaling in a brain region-specific manner may prove a viable mechanism for treating age-related decline in brain function.

A handful of studies have examined potential age-related changes in the NOS-sGC pathway that might contribute to alterations in cGMP synthesis. Findings are highly contradictory with regard to age-related changes in NOS activity. Blum-Degen and colleagues found no difference in NOS activity in aged vs. young human parietal cortex, nucleus accumbens or cerebellum [74]. In the animal literature, however, there are an equal number of findings that report increased, decreased, or no change in NOS activity in aged vs. young hippocampus, cerebellum and cortex, without obvious differences in methodology to account for the discrepant findings [49,75–83]. Reports across species are more consistent with regard to age-related changes in GC expression and/or activity. Expression of sGC decreases between 60 to 90 years of age in human frontal, prefrontal, parietal, and orbital frontal cortex as well as nucleus accumbens [84], and GC activity is reduced in aged vs. young adult rodent hippocampus and cerebellum [49,80]. Consistent with the idea that reduced sGC activity accompanies aging, NO donors—which would stimulate sGC activity—rescue age-related

memory impairments in both rats [85] and crickets [86]. Together, these studies suggest aging may be associated with reduced cGMP synthesis in the brain (Figure 2B).

In contrast to the studies noted above implicating reduced cGMP synthesis via sGC, studies of ANP and BNP would argue for increased cGMP synthesis via pGCs. Studies examining age-related changes in natriuretic peptides (agonists for pGC receptors), have all focused on circulating levels. In humans, circulating levels of ANP are 4 times higher in healthy elderly vs. young adults, and increasing levels correlated with increasing age between 70-102 years of age [87]. In contrast, circulating levels of BNP did not increase with age between 30 and 72 years of age [88]; however, circulating levels of BNP did increase with age after 75 years in humans [89–91], at least in those without dementia [90]. Elevated BNP levels in those over 60 years of age are associated with increased risk of developing a cognitive disorder [90] as well as lower scores and more rapid rates of cognitive decline on tests such as the mini mental state exam (MMSE), Trails B, and logical memory tests [91–94]. It is important to acknowledge that several of these studies also associated higher BNP with increased incidence of CVD, which by itself is a known risk factor for cognitive dysfunction [89,91,92]. That said, 2 studies were able to show that elevated BNP remained independently associated with poor cognitive performance even after adjusting for CVD factors [91,93], and a 3rd study showed an association between elevated BNP and lower MMSE scores in a group of older adults that all had CVD [94]. Taken together, these data suggest that elevated BNP increases risk for poor cognitive performance in the elderly, independent of any effect on CVD. It remains to be determined if ANP and/or BNP may also increase with aging in the brain.

At the level of cGMP itself, the directionality of age-related changes appears to be tissue-specific. Perhaps consistent with the age-related increases in circulating ANP and BNP noted above in humans, cGMP levels are increased in white blood cells taken from aged vs. young adult humans [29,31] and serum taken from aged vs. young adult rodents [33]. In contrast, however, cGMP levels are reduced in platelets taken from aged vs. young adult humans [95]. Reports of cGMP levels in aged human brain are lacking, but studies in rodents have identified decreased cGMP levels in aged vs. young adult cerebellum [25,37,49,96] (but see [80]) and hippocampus [49,80] (but see [25], but not cortex [49]. Glutamate-stimulated cGMP accumulation is also severely compromised in aged vs. young adult rodent hippocampus and cerebellum [49,80,97]. To make matters worse, cGMP-PDE activity appears to be increased in aged vs. young rodent hippocampus and cerebellum [49], possibly due to an upregulation of PDE5A and PDE10A expression [50]. Consistent with a reduction in cGMP levels, PKG activity is also decreased in aged vs. young rat cerebellum [96]. Further, PDE2 [67], PDE3 [68], and PDE5 inhibitors reverse age-related deficits in pCREB, LTP, and/or memory in rodents [98–100] (but see [67]). Thus, increasing cGMP signaling may also prove a viable path forward for treating age-related decline in brain function.

Consistent with the majority of evidence described above that points to reduced cAMP and cGMP signaling in the aged brain, most studies examining age-related changes in CREB have identified reduced function. The vast majority of aging studies that examine CREB signaling focus on the hippocampus, with a few studies focusing on specific subregions of

cortex. In humans, hippocampal CREB levels decreased with increasing age [101]. In rodents, numerous studies report a significant decrease in basal and/or training-induced phosphorylation of CREB (pCREB) in aged vs. young adult rodent hippocampus [36,102–106], with only 1 study suggesting this age-related impairment in pCREB is restricted to cognitively impaired subjects [103]. Further, CREB overexpression into rodent CA1 is sufficient to rescue age-related memory and neurophysiological deficits [107]. In cortex of aged vs. young adult rodents, pCREB appears to be diminished in parietal regions [36] yet increased in prefrontal regions [41,43]. Again, these data suggest a brain region-specific change in cyclic nucleotide signaling accompanies aging, with decreases in hippocampus and some cortical regions but increases specifically in prefrontal cortex

3. Alterations in cyclic nucleotide signaling associated with Alzheimer's Disease, mild cognitive impairment (MCI), and dementia

Studies in patients, rodents, and in vitro models suggest that brain region-specific alterations in cAMP signaling may contribute to dementia-related pathology. Gαs-stimulated AC activity appears to be reduced in hippocampus [108–111], temporal cortex [21,112], frontal cortex [21], occipital cortex [21], and cerebellum [21,109] (but see [112]) of AD or dementia patients vs. controls. Reports of basal and forskolin-stimulated AC activity in patients are somewhat contradictory. The majority of reports suggest AD is accompanied by reductions in basal and/or forskolin-stimulated AC activity in hippocampus [109–111,113] (but see [108]) and temporal cortex [21,114] (but see [112]), but no change in AC activity in cerebellum [21,112] (but see [109]) or occipital cortex [21]. Reports of AC activity in frontal cortex of AD patients are mixed [21,114]. The decreased AC activity that has been measured in tissue from patients does not appear to be driven by increased expression and/or activity of Gαi [109,114,115], reduced expression of Gαs [108], or global reductions in AC expression [116], although specific reductions in AC1 and AC2 (but not AC5, AC6, AC7 or AC8) expression may contribute to the reduced AC activity observed in AD hippocampus and cortex [117,118].

In addition to evidence for reduced cAMP synthesis, there is also evidence for reduced levels of cAMP and cAMP effector molecules in AD patients in select tissues. cAMP levels are lower in polymorphonuclear granulocytes (PMNLs) taken from AD patients vs. age-matched controls [31]. *In vitro* and rodent studies show that overexpression of BACE1 (β-site amyloid precursor protein-cleaving enzyme 1) or infusion of Aβ1–42 are sufficient to decrease cAMP levels in brain lysates [119] and the hippocampus [120], respectively. In a separate line of studies, significant reductions in cAMP binding were measured in the cytosolic fraction, but not particulate fraction, of entorhinal cortex and subiculum taken from AD patients with severe amyloid deposits [121]. A similar trend toward reduced cAMP binding was also observed in cytosolic fractions of hippocampal subfields of AD patients with severe amyloid deposits [121]. Studies in AD patients, rodent models, and *in vitro* models also report reduced PKA expression and/or activity [119,122–126] (but see [112]). Importantly, hippocampal deficits in AD models are reversed when cAMP levels are increased, either by stimulating AC activity with forskolin [127] or, as discussed below, reducing cAMP-PDE expression or activity [120,125,128–134]. Further, the ability of

cAMP-elevating agents to reverse/prevent Aβ1–42-induced hippocampal deficits requires PKA [125,127,131]. Together, these studies strongly suggest that reduced cAMP signaling via PKA is a key feature of AD pathology (Figure 2C).

Reports on HCN channels and Epac are less consistent than those described above for PKA. Reduced expression of HCN1 was found in the temporal lobe of AD patients and experiments in mice and N2A cells suggest a loss of HCN1 function is sufficient to enhance Aβ generation [135]. That said, *in vivo* infusion of Aβ1–42 into rat CA1 increased HCN1 mRNA expression, suggesting either a species difference or a complex negative feedback loop [136]. *In vivo* infusion of Aβ1–42 into rat CA1 also decreased HCN2 mRNA expression [136], which in vitro studies suggest should reduce secretion of Aβ [137]. Isoform-specific changes in the Epacs are also associated with AD. Namely, Epac2 protein expression appears to be reduced while Epac1 expression appears to be increased in frontal cortex of AD patients [138]. The net effect of these isoform-specific changes is yet to be determined; however, it is known that Epac1 activity regulates secretion of the protective soluble form of APP, sAPPα (role of Epac2 not reported, [139,140]). Thus, further studies are required to better understand the role that altered HCN or Epac function may play in the symptomatology of AD.

Localized increases in cAMP signaling may also contribute to the pathology of AD. Increased cAMP levels have been measured in cerebral vessels of AD patients vs. healthy controls [34,35]. Although 2 studies found no difference in CSF cAMP levels of AD patients relative to age-matched controls [141,142], one study found elevated cAMP levels in AD patients [143]. Interestingly, the elevated CSF cAMP levels found in the latter study correlated with CSF tau protein levels [143]. PKA is tightly associated with Tau neurofibrillary tangles (NFTs) [144] and is known to hyperphosphorylate Tau, particularly at residues S198, S199, S214, and S409 [144–147]. Further, Tau-pS214 and Tau-pS409 are only found in AD tissue [144]. Such a localized mechanism may explain why select studies have shown low doses, but not high doses, of PKA inhibitors are able to reverse AD model pathology [148–150]—despite the fact that global PKA activity is largely reduced in AD patients and animal models (as described above, [119,122–126]) and mechanisms that increase cAMP/PKA/CREB signaling appear to prevent and/or reverse AD-related deficits [120,124,125,127–133,151–159]. That said, PKA phosphorylation of Tau does not always promote neurofibrillary tangles. For example, if PKA phosphorylates Tau at S214 after glycogen synthase kinase-3β (GSK-3β) phosphorylates Thr214, then paired helical filaments (PHFs) are formed; however, if PKA phosphorylates S214 before GSK-3β phosphorylates Thr214, then pTau does not form PHFs [160]. Indeed, the PKA phosphorylation of Tau that reduces its affinity for microtubules also reduces its assembly into PHFs [161], perhaps because prior phosphorylation of Tau by PKA makes some Tau sites less accessible to other kinases [162,163].

In addition to reductions in the synthesis of cAMP, there may also be AD-associated alterations in the degradation of cAMP by cAMP-specific or dual-specific PDE families. Increased expression of PDE3 was observed in AD cerebrovessels [155]. Soluble and fibrillary amyloid-β1-42 (Aβ1–42) increased PDE4B expression in cultured microglia, leading to increased neuroinflammation [164]. In early-stage AD patients, PDE4B mRNA

along with PDE4A mRNA expression are increased in entorhinal cortex; however, PDE4A mRNA expression is reduced in frontal cortex and CA2 of late-stage AD patients [156]. PDE4D1 mRNA was doubled in the hippocampus of an AD patient, while PDE4D2 and PDE4D3 remained unchanged and PDE4D5-9 were dramatically reduced [165]. PDE4D mRNA expression was also increased in the putamen of patients with AD [156], but reported as unchanged in temporal cortex of AD patients [141]. PDE7A mRNA is reduced in dentate gyrus (DG) of hippocampus, while PDE8B expression is increased in DG and CA2 of hippocampus [166]. No change in expression was noted for the dual-specific PDE10A in temporal cortex [141] or the dual-specific PDE2A in cortex, hippocampus, striatum or cerebellum of AD patients [167]. Thus, AD-associated changes in PDE expression/activity are clearly isoform and brain-region specific.

Although not all studies identify an upregulation of cAMP-PDE expression or activity in AD patient and model studies, PDE inhibitors have demonstrated efficacy in humans and animals models. High caffeine intake in woman over 65 significantly reduced incident dementia [60], and caffeine reversed cognitive deficits, Tau hyperphosphorylation, and Aβ burden in AD mouse models [168–170]. Although results with the PDE1 inhibitor vinpocetine have been mixed in patients with MCI or AD [171–173], the PDE3 inhibitor cilostazol and various PDE4 inhibitors have been reported as producing beneficial effects in patients with MCI or dementia [55,153,154,174–179]. PDE3 and PDE4 inhibitors, along with PDE2 and PDE7 inhibitors, have also reversed or prevented the onset of deficits in rodents AD models [128–134,155–157,180,181] and *in vitro* models of Aβ cytotoxicity [124,125,134,158,159]. Together, these studies suggest that inhibition of cAMP-PDE activity may prove beneficial in the context of AD and related dementias.

With regard to signals that drive cGMP synthesis, a striking number of studies have associated elevated BNP levels in blood and/or plasma with the existence, severity or risk of developing, mild cognitive impairment (MCI), MCI to AD conversion, AD, and/or vascular dementia (VaD) [88,182–190] (but see [90]). Although several of these studies were confounded by the fact that the patient populations were significantly older than the healthy controls [183–185,187], 2 studies demonstrated elevation in patient BNP levels with no difference in age between healthy controls vs. AD and/or MCI patients [88,182], suggesting a dissociation between age-related and disease-related elevations in BNP. Of course, BNP and ANP are well-known markers of cardiovascular disease (CVD) and CVD is a risk factor in and of itself for dementia. That said, select studies have demonstrated an association between elevated BNP or ANP levels and dementia independent of CVD risk factors [183,184,187,189,190]. Indeed, Tykkynen and colleagues have suggested that these elevated BNP levels may reflect a pathogenic process in the brain and, thus, could be used as a circulating marker of neuronal damage [183]. In this context, it is interesting to note that Hu and colleagues not only found elevated BNP in plasma of MCI and AD patients, they also showed that plasma levels of BNP correlated with CSF levels of Aβ1–42 [186]. Although Llano and colleagues did not find a significant increase in BNP in MCI or AD patients relative to controls, they did identify BNP as a member of a 4-protein signature that was able to differentiate diagnosis [191]. It remains to be determined if MCI and/or AD are associated with BNP changes in brain.

Fewer studies have examined the association between ANP and dementia. ANP levels did not correlate with cognitive function in demented patients [190], but higher levels of ANP were associated with dementia [192,193] or the conversion from MCI to AD/dementia [194]. Unfortunately, studies examining ANP are largely confounded by increased age in the patient population versus controls [192–194]. With regard to the role of ANP in vasoconstriction, it is interesting to note that Schneider and colleagues showed anti-hypertensive therapy in patients with higher baseline ANP—but not low baseline ANP—reduced the rate of converting from MCI to AD, particularly in patients younger than 72 years old [194], suggesting ANP levels may prove a worthwhile patient selection biomarker for use of anti-hypertensive therapies in this context[194].

In addition to the potential for increased signals upstream of pGCs, AD also appears to be associated with increased signaling upstream of sGCs. Relative to healthy age-matched controls, reduced expression of an endogenous NOS inhibitor in CSF [195] and increased NOS activity in platelets of AD patients has been reported [95]. Increased NOS expression has also been noted in hippocampus of AD patients [196] as well as microglia and monocytes treated with Aβ1–40 [197]. Increased NOS activity would provide additional NO that could activate sGC.

These increases in NOS signaling may reflect a compensatory change in response to reduced expression and/or activity of sGCs. Indeed, decreased activity of sGC—but not pGC— was noted in superior temporal cortex of AD patients [198] and decreased activity and/or expression of sGC was noted in reactive astrocytes of AD patients [199] and cultured astrocytes treated with Aβ1–40 or Aβ25–35 [200]. Consistent with the idea that AD is associated with a loss of sGC signaling, cGMP levels are significantly reduced in CSF of AD patients vs. age-matched controls, and lower CSF cGMP levels significantly correlate with worsening performance on the mini mental state exam (MMSE) [141,142] (but see [143]). cGMP levels are also reduced in platelets taken from AD patients [95]. AD mouse models fail to show an upregulation of cGMP levels following NMDA receptor activation in hippocampus [201], and hippocampal slices fail to show an LTP-induced upregulation of cGMP when treated with Aβ1–42 [202]. Importantly, treatments that elevate cGMP signaling rescue microglial inflammation [203], synaptosomal glutamate and glucose transport deficits [204], cytotoxicity [205], and LTP deficits that are caused by Aβ infusion [202] or are found in AD patient synaptosomes [206]. Further, rescue of AD-related deficits by cGMP elevating agents (i.e., NO donors, sGC stimulators, cGMP analogues, PDE inhibitors) occurs in a PKG-dependent manner [202,205,207]. In light of these findings, it is difficult to reconcile studies reporting positive effects of methylene blue in AD, given its well-established ability to decrease cGMP signaling by inhibiting NOS and sGC [208]. That said, methylene blue has a number of molecular and cellular targets beyond cGMP-related targets [208]. Taken together, these studies strongly argue for impairment of sGC/cGMP/PKG signaling in AD (Figure 2C).

In addition to reduced cGMP synthesis via sGC, AD may also be associated with increased cGMP degradation by cGMP-PDEs. A 5-fold increase in expression of the cGMP-specific PDE5A has been reported in temporal cortex of AD patients vs. controls [141], with no significant change found in the expression of the cGMP-specific PDE9A or the dual-specific

PDEs PDE2A and PDE10A [141,167]. Consistent with a disease-related increase in PDE5A expression, PDE5A inhibitors are able to improve LTP deficits in synaptosomes from AD patients [206] as well as reduce cytotoxicity, Aβ burden, Tau hyperphosphorylation, synaptic dysfunction and memory deficits in AD mice [207,209–213] in a PKG-dependent manner [207]. Both the decrease in sGC and the increase in PDE5A noted in AD patients would be expected to specifically reduce cytosolic pools of cGMP, as opposed to membrane/particulate pools of cGMP. This stands in contrast to the fact that protective sAPPα appears to increase cGMP by activating a pGC [214]. While PDE5A is thought to regulate pools of cGMP downstream of sGC, PDE9A is thought to regulate pools of cGMP that are downstream of pGCs [215]. This may explain why PDE9A inhibitors were able to improve cytoxicity, plasticity, and memory deficits in AD mice [216,217], but failed to improve cognition or behavior in AD patients [218]—because a PDE9A inhibitor would not target the cytosolic pools of cGMP that are compromised in AD.

Consistent with the pattern of reduced cAMP and cGMP signaling in AD, studies in patients, rodent models, and *in vitro* models report reduced levels of pCREB [101,119,120,130,132,152,219] (but see [220]), and reduced CRE-mediated transcription [151,221–226]. Importantly, hippocampal deficits in AD models are reversed when CREB is overexpressed [151,152]. Further, the ability of cAMP-elevating agents to reverse/prevent Aβ1–42-induced hippocampal deficits generally corresponds with a restoration of pCREB levels [124,127,131,133,134] (but see, [130]). Together, these studies point to lost CREB function as a key mechanism of cognitive deficits in AD.

4. Alterations in cyclic nucleotide signaling associated with Huntington's Disease

HD results from an expansion of a trinucleotide CAG repeat in the mutated *huntingtin* gene (mHTT). The hallmark symptoms associated with Huntington's disease are uncontrolled choreiform movements that appear to be related to degeneration of medium spiny neurons in the indirect pathway of the striatum. It is increasingly being recognized, however, that depression and cognitive deficits are prevalent in these patients prior to the appearance of motor deficits due to dysfunction in the hippocampus and cortex, and this array of deficits can be found in several HD mouse models. [11].

Findings in patients with HD and HD animal models point to altered cAMP signaling in the striatum, hippocampus and cortex (Figure 2D). In HD patients, decreased cAMP levels have specifically been measured in parietal cortex and lymphoblastoid cells [227]. In HD mouse models, reduced cAMP levels have similarly been measured in cortex and striatum [227], the latter possibly related to a decrease in synthesis by AC5 [228] and/or increased degradation by PDE4 [229]. Although PDE4A mRNA expression does not appear to change in either striatum or cortex of HD mouse models [230], PDE4B expression and PDE4 activity is increased in these regions [229]. This HD-related increase in PDE4 activity appears to be driven by mHTT sequestering DISC1, a protein that would normally bind to and inhibit PDE4B [229]. Reversal studies suggest this increase in striatal PDE4 activity drives the depression-like phenotypes, but not the motoric phenotypes, seen in HD mouse

models [229]. Increased PDE4 activity would be expected to decrease cAMP levels, thereby reducing PKA activity. Indeed, reduced PKA activity in striatum has been reported in HD mice, albeit related to overexpression of PKA regulatory subunits that occurs due to mHTT impairing proteosomal breakdown of those regulatory subunits [231]. In contrast, PKA activity appears to be increased in hippocampus of HD mice, possibly due to a loss of PDE4 signaling [232,233]. Specifically, PDE4AX, but not PDE4A1 or PDE4A5, along with PDE4D1 and PDE4D3 appear to be decreased in hippocampus of HD mice, thus, causing increased PKA activity specifically within the cytosol but not the nucleus [232,233]. Human embryonic stem cell-derived neurons carrying mHTT show reduced expression of a PKA inhibitor, which would also argue for increased PKA activity in the disease state [234].

HD mouse models have also shown reduced cGMP levels in hippocampus, possibly related to a loss of nNOS signaling that could ultimately lead to lower levels of NO-stimulated sGC activity [235]. The HD-related decrease in cAMP and cGMP levels appears to drive compensatory decreases in the expression of PDE10A and PDE1B [228,230], but not PDE5A or PDE9A [235]. Indeed, numerous studies report reductions in PDE10A expression in striatum and select cortical regions in both HD patients [230,236–238] and HD animal models [228,230,239–241], and yet PDE10A inhibitors have repeatedly been shown to rescue behavioral, neurodegenerative, and electrophysiological deficits in HD animal models [228,233,242–244]. The therapeutic benefit of PDE10A inhibitors in HD mice correlates with an ability to increase pCREB in striatum, cortex, and hippocampus [228,233,243,244]. The ability of PDE10A inhibitors to reverse hippocampus-dependent plasticity and memory deficits in HD animal models may be directly related to this increase in hippocampal pCREB, as CRE-dependent transcription is compromised in both patients and HD mice due to a loss of CREB binding protein [245]. The fact that PKA activity is already increased in HD hippocampus [232,233] may suggest that PDE10A inhibitors are increasing pCREB in the hippocampus by restoring PKG activity, although the PKA- vs. PKG-dependent nature of the effect remains to be determined.

5. Alterations in cyclic nucleotide signaling associated with Parkinson's Disease

PD is caused by degeneration of the dopaminergic neurons in the substantia nigra pars compacta that innervate the striatum. It is well understood that patients with PD not only exhibit the classic motor symptoms that define the disease (e.g., resting tremor and bradykinesia), they also demonstrate cognitive deficits, particularly in later stages of the disease [15]. The majority of Parkinson's animal models examining cyclic nucleotide signaling endpoints employ either 6-hydroxydopamine (6-OHDA) or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) to lesion dopaminergic neurons in the substantia nigra pars compacta (SNpc) [246]. 6-OHDA must be stereotaxically injected directly into the SNpc, where it is taken into neurons by the dopamine transporter (DAT) and accumulated in the mitochondria [246]. In contrast, MPTP is delivered systemically because it crosses the blood brain barrier. MPTP is taken up by astrocytes and converted to the active molecule MPP+, which is then taken up by the DAT on neurons and collected in both mitochondria and synaptic vesicles [246]. MPTP is generally regarded as the stronger of the

2 toxin models given evidence in humans that it creates a syndrome representing idiopathic parkinsonism [246]. Although both models lesion dopaminergic input to the striatum, they appear to produce opposite effects on striatal cyclic nucleotide signaling.

Studies in patients have reported increases in cyclic nucleotide signaling, particularly that via cGMP, being associated with pharmacological and electrophysiological therapeutic approaches. A meta-analysis of 13 articles showed that PD risk is reduced with higher consumption of caffeine, a compound able to increase cAMP and cGMP by inhibiting PDEs [247]. This might suggest that increased PDE activity is a driver of PD; however, studies in patients implicate reduced expression of PDE4D [248], PDE8B [249], and PDE10A [250] in the pathology of parkinsonism. Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is used to treat patients with PD, and this treatment transiently increases cGMP signaling in the striatum of PD patients [251–253]. Unfortunately, these studies did not include healthy controls, so it is unclear if this transient increase in cGMP seen in patients might reflect a reversal of a disease-related reduction in striatal cGMP signaling. One study identified reduced NOS expression in the striatum of PD patients, which could lead to less cGMP production via sGCs [254]. L-DOPA, a drug used to treat PD patients by restoring dopamine levels, also increases cGMP levels as measured in serum [255,256] (but not plasma [257]) and CSF [257] of patients.

The fact that therapeutic efficacy correlates with increased cGMP might suggest that reduced cGMP signaling is inherent to PD pathology; however, direct evidence is lacking. Several studies show there are no basal differences in CSF cGMP levels between untreated PD patients and healthy controls [258–260]. In contrast, findings with regard to CSF cAMP levels are mixed with one study finding no change [259], and one study finding reduced cAMP in CSF of PD patients vs. controls [260]. The suggestion of reduced cAMP signal transduction in PD is supported by *in vitro* studies showing disease-related mutations in LRRK2 and alpha synuclein interfere with activity of PKA and CREB, respectively [261,262]. Thus, more work is needed in PD patient samples to understand whether a brain region-specific reduction in cAMP or cGMP signaling may be inherent to the disease state or if increasing cyclic nucleotide signaling might simply be a means of providing therapeutic relief by compensating for signaling dysfunction elsewhere.

Generally speaking, experiments examining the striatal effects of the 6-OHDA model more readily argue for decreased cGMP and increased cAMP in striatum being associated with parkinsonism. 6-OHDA lesions of the substantia nigra appear to reduce cGMP in the striatum and globus pallidus (GP) (similar trend in cortex) while increasing cAMP in the striatum [263–265]. The downregulation of striatal cGMP produced by 6-OHDA may be related to reduced NOS activity [265,266], which could lead to lower levels of NO and reduced activation of sGC. The downregulation of striatal cGMP by 6-OHDA may also be related to increased PDE1B expression [264,265]. In contrast, the 6-OHDA-induced increase in cAMP may be related to lesion-induced decreases in PDE10A expression [264] that are similar to those measured in PD patients [250]. Such a bimodal regulation of PDE1B vs. PDE10A has previously been measured in mouse models unrelated to PD, with decreased PDE1B expression corresponding to increased PDE10A expression [267,268]. Such a bimodal regulation may be related to the fact that PDE1B appears to be enriched in the

striatonigral pathway while PDE10A appears to be enriched in the striatopallidal pathway [269]. Taken together, these results might suggest that 6-OHDA 1) reduces cGMP specifically in the striatonigral pathway via downregulation of NOS and upregulation of PDE1B, and 2) increases cAMP specifically in the striatopallidal pathway by decreasing PDE10A expression.

Results from experiments using the MPTP model are mixed in terms of implicating increased vs. decreased cyclic nucleotide signaling as a root cause of pathology. In mice, *in vivo* MPTP appears to increase NOS expression/activity, GCβ1 expression, GC activity, and cGMP levels in striatum and midbrain [270,271]. Increased striatal cGMP signaling in response to MPTP would stand in stark contrast to the decreased cGMP signaling that is caused by 6- OHDA lesions, as described above. In rats, however, MPTP reduced cGMP and cAMP levels in striatum [272]—the former effect in concert with effects of 6-OHDA but the latter effect, again, standing in contrast. Importantly, MPTP-induced deficits in rat striatal cAMP and cGMP levels were reversed by the PDE1 inhibitor vinpocetine, as were the MPTP-induced motoric deficits [272]. Further, increasing cGMP signaling via PKG using vasonatrin, a manmade natriuretic peptide, reversed MPP+-induced cytotoxicity of cultured mouse striatal neurons [273]. Some attenuation of MPTP neurotoxicity was also achieved with a low dose of rolipram, an inhibitor of the cAMP-specific PDE4 isoforms [274]. Thus, while reports of the direct effect of MPTP on cyclic nucleotide levels somewhat conflict with each other and those reported for the 6-OHDA model, they do seem to parallel findings in humans in terms of showing a beneficial effect of drugs that increase cGMP and/or cAMP signaling.

6. Summary and conclusions

In summary, aging and age-related diseases appear to be associated with region and, in some cases, subcellular compartment-specific changes in cAMP and cGMP signaling. For example, aging and AD are associated with decreased cAMP signaling in hippocampus, yet select studies implicate increased cAMP signaling in prefrontal cortex and cerebral vessels, respectively. In contrast, HD is associated with increased cAMP signaling in the hippocampus and decreased cAMP signaling in cortex and striatum. This suggests that cyclic nucleotide signaling will have to be targeted in a region-specific manner if therapeutic efficacy is to be obtained in absence of side effects. Adding an additional level of complexity are reports suggesting that cyclic nucleotide changes may be occurring only within select subcellular compartments, such as in the case of AD studies identifying disturbances in cytosolic but not membrane compartments.

Fortunately, it may be possible to target cyclic nucleotide signaling in both a brain region-specific and a compartment-specific manner. For example, PDE11A is selectively expressed in the hippocampal formation [50]. Further, it is enriched in cytosolic over membrane and nuclear compartments [275], and its relative enrichment in cytosol can be amplified by disrupting PDE11A homodimerization [276]. Thus, a PDE11-targeted therapeutic would preferentially modulate cAMP and cGMP signaling within the cytosol of the hippocampus, specifically within CA1 and subiculum. This, coupled with the fact that PDE11A plays a key role in social memory formation, mood stabilization, and social interaction behaviors [276–

279], suggests PDE11A may be an ideal therapeutic target to address cyclic nucleotide disturbances in a disease like AD. On the other hand, PDE10A is enriched in the striatum with little expression in the hippocampus. So, while PDE10A would not be a likely candidate for AD treatment, it would be an ideal mechanism for targeting the striatal cAMP deficits that are seen in HD patients because it would not exacerbate the heightened hippocampal cAMP signals that may be associated with that disease. Promisingly, drugs that increase cyclic nucleotide signaling, particularly PDE inhibitors, have demonstrated promise in both the clinic and animal models, suggesting the viability of targeting this signal transduction system for the treatment of age-related cognitive decline and age-related diseases.

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HIGHLIGHTS

- Aging is associated with decreased cAMP/cGMP signaling in most brain regions but increased cAMP signaling in prefrontal cortex and cerebral microvessels
- Alzheimer's is associated with decreased cAMP/cGMP in hippocampus and temporal cortex but increased cAMP in microvessels
- Huntington's is associated with decreased cAMP/cGMP in striatum and cortex but increased cAMP signaling in hippocampus
- Therapeutic efficacy in Parkinson's correlates with increasing cGMP signaling
- PDE inhibitors rescue deficits associated with aging, Alzheimer's, Huntington's, and Parkinson's Disease

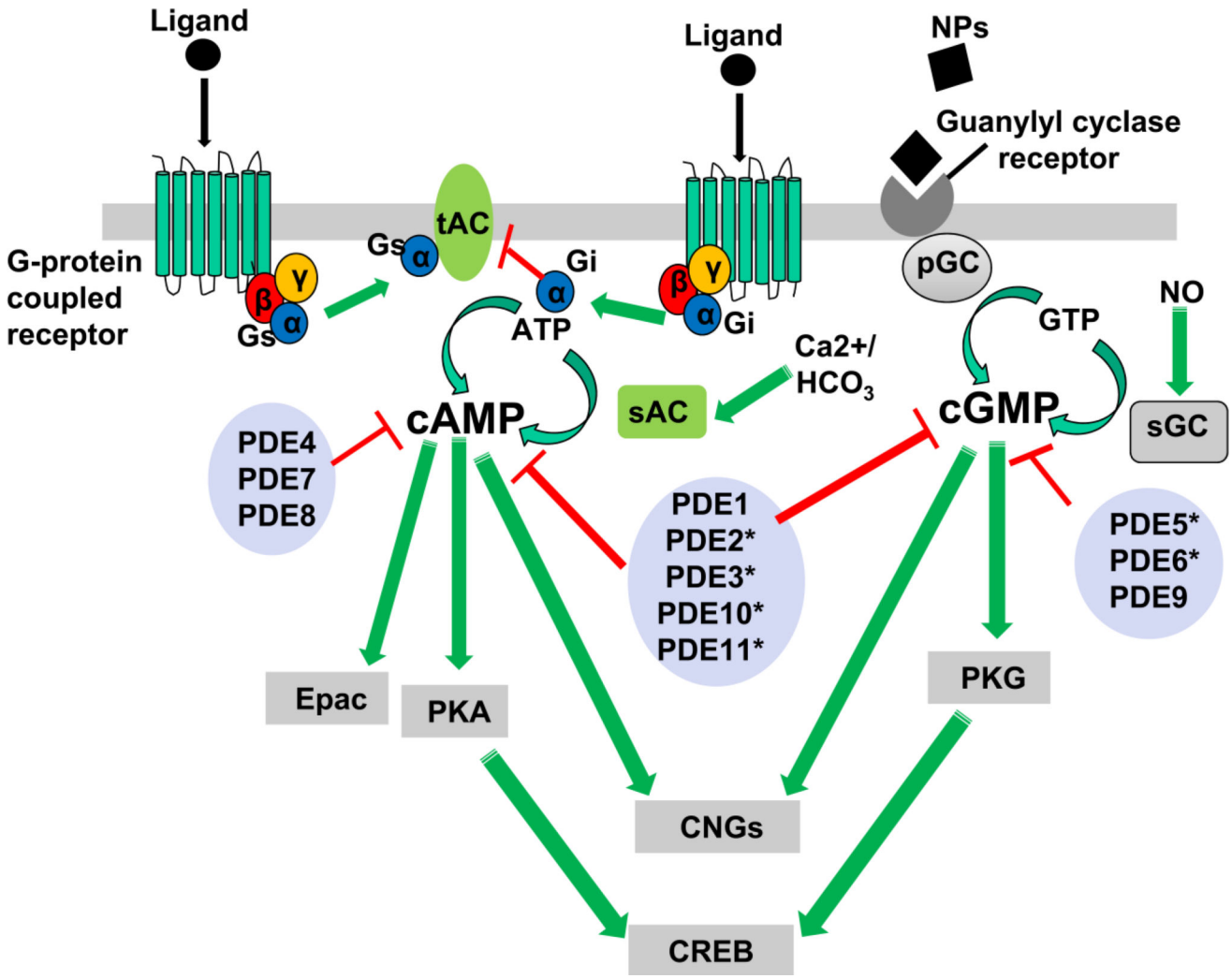

Figure 1.

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, and 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.

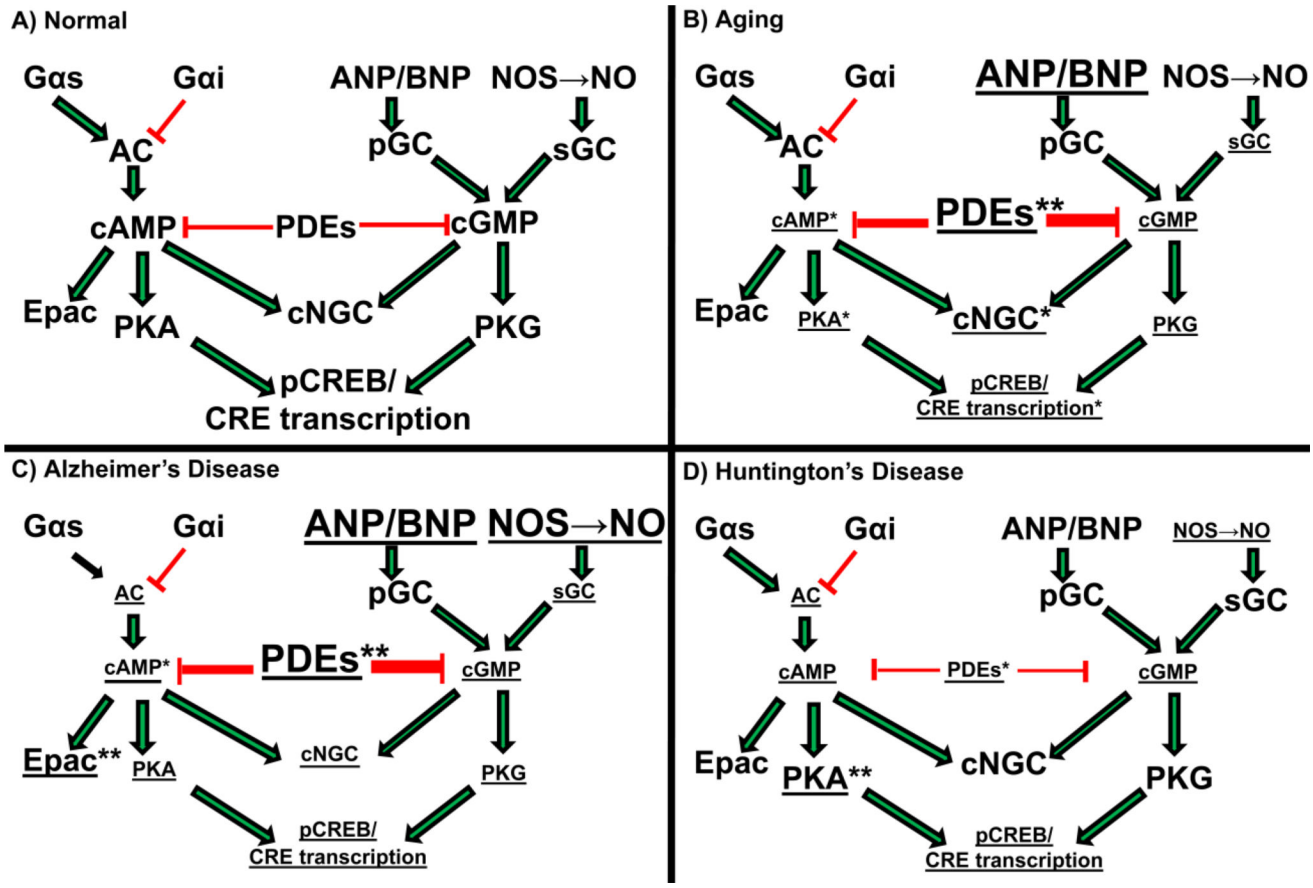

Figure 2.

Aging, Alzheimer's Disease, and Huntington's Disease are generally associated with reduced cAMP and cGMP signaling in brain compared to normal levels. A) Normal signaling seen in young adult brain. Targets that appear to change in response to age or disease relative to this baseline are underscored in subsequent panels, and increases/decreases are indicated by a change in the relative font size (e.g., smaller font means decreases were noted). B) Studies in most brain regions indicate that aging is associated with reductions in basal or stimulated cAMP levels, PKA activity, soluble guanylyl cyclase (sGC) activity, cGMP levels, PKG activity, and CREB activity (as measured by phosphorylation or rates of CRE-dependent transcription) and increased phosphodiesterase (PDE) activity. C) Relative to the healthy age-matched controls, which already show reduced cAMP/cGMP signaling as outlined in panel B, Alzheimer's disease patients/models demonstrate even further reductions in the aforementioned targets as well as reductions in adenylyl cyclase (AC) activity and cyclic nucleotide gated channels (cNGC). D) Similar, changes can also be seen in Huntington's Disease patients/models, with the notable exception that most studies report decreases in PDE expression/activity. *opposite effect noted in select tissues (e.g., increased cAMP signaling in aging prefrontal cortex or HD hippocampus, specifically)—see main text. **age/disease-related changes have been noted, but directionality (increase vs. decrease) depends on specific isoform and/or brain region—see main text.

Table

Reported differences in phosphodiesterases (PDEs) seen in aged vs. young adults

	Hippocampus	Cortex	Striatum	Cerebellum	other
PDE1	increased protein expression of select 1C isoforms [50]	no change 1A, 1B, or 1C mRNA [50]	no change 1A, 1B, or 1C mRNA [50]	no change 1A, 1B, or 1C mRNA [50]	
PDE2	no change 2A mRNA [50]	no change 2A mRNA [50]	decreased 2A mRNA [50]	no change 2A mRNA [50]	
PDE3	no change 3A or 3B mRNA [50]	no change 3A or 3B mRNA [50]	no change 3A or 3B mRNA [50]	no change 3A or 3B mRNA [50]	
PDE4	no change 4A, 4B or 4D mRNA; decreased PDE4 binding in situ but not in cytosolic fractions [50,53,56,57]	decreased 4D but not 4A or 4B mRNA in rat; decreased PDE4A5 protein in monkey in dlPFC; decreased PDE4 binding in rat and monkey; decreased PDE4 activity rat [50,51,53,56,57]	decreased 4A mRNA but no change 4B or 4D mRNA; decreased PDE4 binding in rat and monkey; decreased PDE4 activity rat [50,53,56,57]	decreased 4D mRNA but no change 4A or 4B mRNA; decreased PDE4 binding in rat but no change monkey; decreased PDE4 activity rat [50,53,56,57]	decreased PDE4 binding in thalamus, SN, & BS; increased PDE4 activity in basal forebrain [56,58]
PDE5	no change 5A mRNA [50]	no change 5A mRNA [50]	no change 5A mRNA [50]	increased 5A mRNA [50]	
PDE7	no change 7A mRNA [50]	decreased 7A mRNA [50]	no change 7A mRNA [50]	no change 7A mRNA [50]	SNP linked to age-related cognitive [54]
PDE8	increased 8A and 8B mRNA and protein expression, with possible change in compartmentalization [50]	no change 8A or 8B mRNA [50]	increased 8A mRNA, no change 8B mRNA [50]	no change 8A or 8B mRNA [50]	
PDE9	no change 9A mRNA [50]	no change 9A mRNA [50]	no change 9A mRNA [50]	no change 9A mRNA [50]	
PDE10	no change 10A mRNA [50]	no change 10A mRNA [50]	no change 10A mRNA [50]	increased 10A mRNA [50]	
PDE11	increased 11A mRNA and protein expression with possible change in compartmentalization [50]	no change 11A mRNA [50]	no change 11A mRNA [50]	no change 11A mRNA [50]	
PDE activity	increased high (but not low) Km cAMP-PDE activity; large increase in cGMP-PDE activity [48,49]	increased high (but not low) Km cAMP-PDE activity; small increase in cGMP-PDE activity [48,49], but see [280]	findings conflict: 1 study no change in high or low Km cAMP-PDE activity; 1 study reduced cAMP-PDE activity [48,281]	large increase in cGMP-PDE activity [49]	no change cAMP-PDE or cGMP-PDE activity in superior cervical ganglia or serum [33,282]

dlPFC--dorsolateral prefrontal cortex; SN--substantia nigra; BS--brainstem; SNP--single nucleotide polymorphism