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Review

Herbs to curb cyclic nucleotide phosphodiesterase and their potential role in Alzheimer's disease

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ABSTRACT

Cyclic nucleotides *viz*., cAMP/cGMP has been well known to play important role in cellular function and deficiency in their levels has been implicated in the pathogenesis of various neurodegenerative disorders including Alzheimer's disease (AD). Phosphodiesterases (PDE) are the enzymes involved in the metabolism of cyclic nucleotides and the inhibition of phosphodiesterases is considered to be viable strategy to restore the level of cyclic nucleotides and their functions in the brain. Various synthetic PDE inhibitors had been used clinically for various disorders and also suggested to be useful candidates for treating neurological disorders. However, side effects of these synthetic PDE inhibitors have limited their use in clinical practice. Natural plant extracts or their bio-active compounds are considered to be safe and are widely acceptable. During the last decade, many plant extracts or their bio-active compounds were tested pre-clinically for PDE inhibitory activity and are reported to be equally potent in inhibiting PDE's, as that of synthetic compounds. The present review is aimed to discuss the potential plant extract/compounds with PDE inhibitory activity and critically discuss their potential role in Alzheimer's disease.

1. Introduction

Alzheimer's disease (AD), is an age-related progressive neurodegenerative disease, characterized by progressive deterioration in cognitive functions, behavioral changes and decline in daily living activities (Fratiglioni et al., 1999). Aging is linked with alteration in the brain neurotransmitter levels and second messenger systems directly involved in signal transduction. Various signal transduction events in brain like calcium mobilization, phosphatidylinositol breakdown, cyclic nucleotides formation and neurotransmitter have been found to be deficient in the aged patients of AD (Deshmukh et al., 2009; Fülöp and Seres, 1994). Cyclic nucleotide has been demonstrated to play important role in cognitive and motar functions (Bollen and Prickaerts, 2012). Interestingly alteration in the level of cyclic nucleotides *viz*., cAMP and cGMP has been demonstrated to occur in various neurological disorder including Alzheimer's disease (McPhee et al., 2005). Cyclic nucleotide Phosphodiesterases (PDEs) represents a super family of enzymes specialized in the degradation of cAMP and cGMP (feedback mechanism of cAMP and cGMP) (Francis et al., 2000; Mika et al., 2012). Phosphodiesterases inhibitors are effectively used clinically for erectile dysfunction and claimed to be novel target site for the treatment of various peripheral and neurological disorder including Asthma, COPD and CVS disorders (Bender and Beavo, 2006; Ghosh et al., 2009). Selective PDE4 inhibitor, Rolipram and its synthetic analogues have been reported to beneficial in AD, but these drugs failed in clinical trials due their unacceptable adverse effects (*i.e.*, nausea and vomiting) (Lipworth, 2005; O'Donnell and

Abbreviations: cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; AD, Alzheimer's disease; PDE, phosphodiesterases; Aβ, amyloid beta; NFTs, neurofibrillary tangles; FAD, familial Alzheimer's disease; SAD, sporadic Alzheimer's disease; APP, amyloid precursor protein; PS-1, presenilin; Aβ oligomer, amyloid beta oligomer; AβPP, amyloid βprecursor protein; sAβPP, soluble amyloid beta precursor protein; ROS, reactive oxygen species; IL-1, interleukin-1; IL-6, interleukin-6; TNFα, tumor necrosis factor alpha; GDP, guanosine diphosphate; GTP, guanosine triphosphate; AC, adenylyl cyclase; GC, guanylyl cyclase; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; 5′AMP, 5′adenosine monophosphate; PDE, phosphodiesterase; cGMP, cyclic guanosine monophosphate; 5′GMP, 5′guanosine monophosphate; EPAC, exchange protein activated cAMP; ERK, extracellular signal- regulated kinase; PKA, protein kinase A; PKG, protein kinase G; CREB, cyclic AMP response element binding protein; BDNF, brain derived neurotrophic factor; NGF, nerve growth factor.

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Zhang, 2004). Moreover, PDE inhibitors are under clinical development for the treatment of Alzheimer's disease. Recently, natural plants extracts and their bio-active compounds has also been demonstrated to moderate the levels of cyclic nucleotide through inhibition of phosphodiesterases (Rahimi et al., 2010). In recent years, there is an unprecedented development in herbal medicines and these are gaining popularity day by day for the treatment of various neurodegenerative disorders including Alzheimer's disease (Divino da Rocha et al., 2011; Howes and Houghton, 2003; Shu, 1998). Herbal PDE inhibitors are under clinical development for the treatment of Alzheimer's disease. Zembrin and Resveratrol are herbal phosphodiesterases inhibitor in the clinical development for the treatment of Alzheimer's disease (www.clinicaltrial.gov). It has been reported that natural plant extracts and their bio-active compound, preclinically possess phosphodiesterases inhibitory potential and show neuroprotective action by improving cognitive function in AD, and other neurodegenerative disorders (Rahimi et al., 2010; Temkitthawon et al., 2008). The present review is aimed to discuss the potential role of plant extract/compounds with PDE inhibitory activity and critically discuss their putative role in Alzheimer's disease.

2. Neurobiology of Alzheimer's disease

Alzheimer's disease (AD), is the most common dementia in the elderly population (65 years) associated with progressive decline in neuronal degeneration of the CNS (Praticò, 2008). Currently approximately 33.9 million individuals suffer with AD worldwide and 5.3 million in the United States, and is anticipated that prevalence will triple over the next 40 years due to demographic changes and longer life expectancies (Barnes and Yaffe, 2011). The pathological hallmarks of AD are extracellular deposit of amyloid plaques, which are primarily composed Amyloid beta (Aβ) peptide (Marsden et al., 2011) and intracellular accumulation of neurofibrillary tangles (NFTs) composed of hyper phosphorylated tau protein (Holtzman et al., 2011).

Alzheimer's disease is classified into two types based on etiology,onset of symptoms, pathophysiological, biochemical and genetic alterations into familial Alzheimer's disease (FAD) and Sporadic Alzheimer's disease (SAD) (Michon, 2009). Familial AD is caused by mutations in the amyloid precursor protein (APP) gene on chromosome 21, in the presenilin (PS-1) gene on chromosome 14 and in the (PS-2) gene on the chromosome 1 (Bennett et al., 2009). The genetic abnormalities on chromosome 1, 14 and 21 are all characterized by the permanent generation of Amyloid beta $A\beta_{(1-40)}$ and in particular $A\beta_{(1-42)}$, beginning early in life (Schwab and McGeer, 2008). In Sporadic AD, disturbed metabolism of APP leads to defective clearance of β amyloid and generate a cascade of events including hyperphosphorylated in tau (τ) leading to breakdown of microtubular assembly and synaptic failure (Terwel et al., 2002; Villemagne et al., 2013). Growing evidence has been demonstrated that oxidative stress is an important factor in SAD (Ramamoorthy et al., 2012). Oxidative damage predominately involves DNA damage, protein oxidation, lipid peroxidation and advanced glycosylation end products. On the other hand neuroinflammatory components such as cytokines, eicosanoids plays important role in, AD pathology as shown in Fig. 1 (Hensley, 2010; Naderi et al., 2006).

Moreover, SAD is associated with a multitude of inherent changes in cerebral glucose/energy metabolism, its control, and related pathways at cellular, molecular and genetic levels (Placanica et al., 2009). Further ageing has also been linked with alteration in brain neurotransmitter levels and second messenger system directly involved in signal transduction. Various signal transduction events that are deficient in brain include calcium mobilization, phosphatidylinositol breakdown, cyclic nucleotide formation and neurotransmitter during AD (Deshmukh et al., 2009; Fülöp and Seres, 1994). Cyclic nucleotide has been demonstrated to play important role in cognitive function. Interestingly alteration in the level of cyclic nucleotide *viz.*, cAMP and cGMP has been demonstrated to occur in Alzheimer's disease (Bender and Beavo, 2006; Sharma et al., 2013).

3. Cyclic nucleotides and their signaling mechanism

Cyclic nucleotide (cAMP/cGMP) second messengers have been reported to play significant role in the regulation of cellular functions such as signal transduction and synaptic transmission of various neurotransmitters in brain (Greengard, 2001; Majeuiski and Musgrave, 1995). Cyclic nucleotides *i.e.*, cAMP/cGMP facilitate bonding to their target enzymes, protein kinase A (PKA) and protein kinase G (PKG) (Kopperud et al., 2003). Out of the several proposed mechanisms, cyclic nucleotide mediated trans activation of cyclic AMP response element binding protein (CREB) (Lu et al., 1999), and brain derived neurotrophic factor (BDNF) (Oliveira et al., 2006), has been reported to play a significant role in cognitive functions (Baquet et al., 2005).

CREB is an activity inducible transcription factor and binding of multiple kinases to Serine-133 (Ser-133) region results in the activation CREB. CREB mediated transcriptional activity has been shown to enhance synaptic plasticity, neuronal growth and development (Delghandi et al., 2005). Moreover CREB activation has also been reported to increase the activities of various neurotrophic factors such as BDNF (Lonze and Ginty, 2002), nerve growth factor (NGF), neurotrophin-3, neurotrophin-4 *etc.* Which are reported to have profound neuroprotective actions as shown in Fig. 2 (Merz et al., 2011; Puerta et al., 2010).

Thus, it is clear that the restoration of cyclic nucleotides would serve as a novel strategy to improve synaptic plasticity and cognitive functions. One such strategy is to inhibit cyclic nucleotide phosphodiesterases, which can enhance the cyclic nucleotide levels.

3.1. Phosphodiesterases

Cyclic nucleotide Phosphodiesterases (PDEs) are the key enzymes within the intracellular signal transduction cascade that follow activation of many types of membrane-bound receptors. PDEs degrade cyclic adenosine monophosphate (cAMP) and/cyclic guanosine monophosphate (cGMP) by hydrolysis of phosphodiester bonds as shown in Fig. 3. Thereby; they regulate intracellular levels of these ubiquitous second messengers (Greengard, 2001; Lesch and Lerer, 1991) (Fig 3).

Human genome encode 21 PDE genes that are categorized into 11 families based on protein sequence, structure, substrate specificity, enzymatic properties, sensitivity to selective inhibitors, and tissue distribution (Sharma et al., 2013). Based upon substrate specificity as shown in Fig. 4 the PDE family is classified as cAMP specific (PDEs 4, 7, 8); cGMP specific (PDEs 5, 6, 9) and dual specificity (PDEs 1, 2, 3, 10, 11) (Bender and Beavo, 2006) (Fig 4).

PDEs are expressed in multiple tissues, including the brain and spinal cord. Although some PDE family members have limited tissue specificity and central nervous system (CNS) distribution, individual neurons frequently express multiple PDEs as shown in Table 1 (Sharma et al., 2013).

3.2. Cyclic nucleotide phosphodiesterases and Alzheimer's disease

Alzheimer's disease is associated with changes in expression of PDE1, PDE4, PDE9, and PDE10 in the brain tissues (Bollen and

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