A Review on the Potential Benefits of Phosphodiesterase Inhibitors in Various Models of Toxicities in Animals

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ABSTRACT

Phosphodiesterase (PDE) enzymes are presented in nearly all cells and inhibitors of these enzymes have various pharmacological properties including cardiotoxic, vasodilator, smooth muscle relaxant, antidepressant, antithrombotic, bronchodilator, anti-inflammatory and enhancer of cognitive function. According to their different usage and the wide expression of PDE enzyme in the body screening the applications of PDE inhibitors (PDEI) may help to find effective pharmacological therapy with the least adverse effect for treatment of different toxicities. In this study we reviewed the protective effects of PDEI in different toxicities caused by toxins or drugs including cardiovascular toxicity, neurotoxicity, hepatotoxicity, nephrotoxicity, gastric mucosal damage and their beneficial role in inflammatory bowel disease and diabetes mellitus. Most of included studies were in animal. Results indicate that 3 families of PDEIs (3, 4, 5) are the most common drugs that have been used as compared to other types of PDEIs in treatment of toxicities. It is required to conduct human and clinical examinations on anti-toxicity effects of PDEIs.

Key words: Phosphodiesterase inhibitors, toxicity, cAMP, cGMP, adverse effects

INTRODUCTION

The cAMP and cGMP are intracellular second messengers that involved in many physiological actions such as vascular resistance, cardiac output, visceral motility, immune response, inflammation, vision and reproduction (Gosh et al., 2009). The cellular content and also biological action of cAMP and cGMP are regulated by the balance between synthesizing enzyme adenylate cyclase and guanylate cyclase, respectively and catabolizing enzymes, the 3', 5'-cyclic nucleotide Phosphodiesterase (PDE) that are able to hydrolyze bond in these cyclic nucleotide yielding 5'-nucleotides (Dousa, 1999). The family of PDE enzymes are categorized into almost 11 based on localization, structure, substrate specificity, enzymatic properties and sensitivity to selective inhibitors (Kotera et al., 2005; Beavo et al., 1994; Uckert et al., 2001). Some of these enzymes hydrolyze only cAMP (PDE4, PDE7, PDE8) and some others hydrolyze only cGMP (PDE5, PDE3, PDE9) and others have mixed specificity (PDE1, PDE2, PDE3, PDE10, PDE11) (Boswell-Smith et al., 2006; Ghosh et al., 2009). Based on expression of PDE isoenzyme in nearly all tissue, inhibitors of these enzymes have effective therapeutic actions in many diseases such as
dementia, depression, schizophrenia (Jeon et al., 2005), congestive heart failure (Hood, 1989; Arnallem et al., 2005), diabetes (Milani et al., 2005), asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, multiple sclerosis, Crohn's disease (Huang et al., 2001), erectile dysfunction in men (Rotella, 2002) and persistent pulmonary hypertension of the newborn (Travadi and Patole, 2003). According to Table 1, they also have positive roles in protection of toxicants that are caused by toxins or some drugs. PDE3 enzyme hydrolysis both cAMP and cGMP, but its affinity for cAMP is 10 times higher than cGMP (Lugnier, 2006). It is mainly expressed in heart, liver, platelet and adipocytes (Harrison et al., 1986; Macphee et al., 1986; Degerman et al., 1987). So inhibitors of this enzyme such as amrinone and milrinone may be useful in treatment of drug-induced cardiovascular toxicities. PDE4 a cAMP-PDE is mainly expressed in inflammatory cells, airway smooth muscle, brain and cardiovascular tissue (Muller et al., 1996). According to Table 1, inhibitors of this enzyme like rolipram, IBMX (3-isobutyl-1-methylxanthine) and a novel inhibitor (CDP840) have beneficial effects in treatment and prevention of neurologic damages and airway diseases are caused by toxins (MPTP, malathion, quinolinic acid, LPS of Ecoli, ozon, brucella melitensis). PDE5 a cGMP specific PDE is mainly expressed in platelets and vascular smooth muscles, heart, placenta, skeletal muscle, pancreas and to a much lesser extent in the brain, liver, and lung (Kotera et al., 2000; Ghosh et al., 2009). So, PDE 5 inhibitors according to Table 1 have wide variety applications in toxicities such as antioxidant effect, amelioration of nephrotoxic damage, protection against serotonin depletion, protection of gastric mucosa against non steroidal inflammatory drugs (NSAIDs), amelioration of hepatic damages, cardio protection, overcoming sexual dysfunction caused by SSRIs. The PDEIs have been even found in herbal products (Rahimi et al., 2010).

In this study, we reviewed the protective role of 3 families of PDEIs (3,4,5) in cardiovascular toxicity, neurotoxicity, hepatotoxicity, nephrotoxicity, gastric mucosal damage, inflammation and oxidative stress.

Cardioprotective effect: Bupivacaine causes cardiovascular toxicity by alteration of Ca²⁺ release from cardiac sarcoplasmic reticulum (Lynch, 1986; Coyle and Sperelakis, 1987) and blockade of cardiac sodium channel (Clarkson and Hondeghem, 1985). Amrinone by inhibition of PDE3 in heart muscle increases intracellular cAMP thereby facilitates slow Ca²⁺ inward via activating various protein kinases (Lindeman et al., 1983; Kondo et al., 1983) and enhances sodium currents via phosphorylation of myosin kinase (Ikebe and Reardon, 1990). So this drug can be effective in situations that sympathomimetics are ineffective. It was shown that amrinone is superior to epinephrine in reversing bupivacaine-induced cardiovascular depression (Saitoh et al., 1995).

β-Blockers and calcium channel blockers have similar toxic effects because, both of them inhibit calcium entry to cells by different mechanisms. Calcium channel blockers maintain the L-type calcium channels in a closed state and β-blockers close these channels by decreasing cAMP levels in cells and thereby inhibition of phosphorylation of L-type calcium channels (Sperelakis and Wahler, 1988; DeWitt and Waksman, 2004). According to Table 1, PDE3 inhibitors have therapeutic values in treatment of β-blocker poisoning and have beneficial effects on acute-drug induced heart failure by their inotropic effects.

Doxorubicine is a potent chemotherapeutic agent used in treatment of hematologic and solid tumor malignancies (Bristow et al., 1978) but its usage has been limited because of cardiotoxicity (Lefrak et al., 1973). The exact mechanism of this adverse effect is not clear but some studies showed that PDE5 inhibitors have cardioprotective effect against doxorubicine-induced cardiomyopathy (Fisher et al., 2005; Koka et al., 2010).

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**Neuroprotective effect:** MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) is a dopaminergic neurotoxin. PDE4 inhibitors like rolipram can reduce MPTP-induced dopamine depletion in the striatum by activating cAMP-dependent protein kinase (PKA/cAMP) regulatory element-binding protein (CREB) signaling pathway. Furthermore, there are two different mechanisms for its neuroprotective effect:

- It blocks the induction of inducible nitric oxide synthase and thus protects against MPTP toxicity (Beshay et al., 2001; Dehmer et al., 2000)
- By blocking microglial production of superoxide makes resistance to MPTP neurotoxicity because of NADPH oxidase deficiency (Wu et al., 2003)

So, it inhibits inflammation and improves the survival of dopaminergic neurons and might be useful therapeutic agent for parkinson disease.

Shiga toxin produced in Escherichia coli infection causes brain damage by thrombotic microangiopathy that results from the synergistic action of this toxin and proinflammatory cytokines (tumor necrosis factor and interleukin1β) (Matussek et al., 2003; Paton and Paton, 1998; Obrig, 1997). PDEs reduce production of proinflammatory cytokines (Essayan, 2001) and have a stabilizing effect on blood-brain barrier (Folcik et al., 1999) and antithrombotic effect (Macphee et al., 1986). Thus these drugs might have effective role in prevention of neurotoxicity of Shiga toxin.

In quinolinic acid lesion model of striatal excitotoxicity, the activity of cAMP responsive element-binding protein is decreased like what is happening in Huntingtons disease (HD) (DeMarch et al., 2007; Steffan et al., 2000). Thus drugs that counteract with loss of function of CREB can have therapeutic value for treatment of neurodegenerative disease like HD. According to some studies, PDE4 inhibitors can increase CREB phosphorylation (Jacob et al., 2004) and CREB is required for the survival of adult CNS neurons (Azadbar et al., 2009). So, PDE4 inhibitors like rolipram might be considered as therapeutic agent for HD. 3, 4-Methylenedioxyxymethamphetamine (MDMA) is a selective 5-hydroxytryptamine (5-HT) neurotoxin in rats (Green et al., 2003). This neurotoxicity is caused by a decline in the activity of tryptophan hydroxylase and consequently a decrease in the content of 5-HT (Commings et al., 1987). Puerta et al. (2009) showed that PDE5 inhibitors via increasing cGMP production protect this toxicity by a mechanism that involves cGMP/PKG pathway and the mitochondrial ATP-sensitive K⁺ channel.

**Hepatoprotective effect:** Some studies have shown that increased level of cyclic adenosine mono phosphate (cAMP) is associated with suppression of the production of tumor necrosis factor-α (TNF-α) and several cytokines (Torphy, 1998) that are responsible for induction of hepatic injury (Decker, 1990). Furthermore, high concentration of cAMP can reduces the release of the reactive oxygen species (Lad et al., 1985) and can inhibit degranulation and proliferation of inflammatory cells (Matsushashi et al., 2005). Matsushashi et al. (2005) showed that drugs capable of suppressing the production of proinflammatory cytokines including PDE inhibitors may be useful for treatment of hepatotoxicity of thioacetamide.

In CCL4-induced hepatotoxicity, increasing the level of cGMP by PDE5 inhibitors can stimulate BK (Ca²⁺) channel activity and through a negative feedback limits Ca²⁺ influx into excitable cells (Wu, 2003). Some study showed that limiting Ca²⁺ influx into hepatocyte by calcium channel blockers ameliorated hepatic injury (Landon et al., 1986; Romero et al., 1994). According to this result, PDE5 inhibitors can demonstrate hepatoprotective effects.
Nephroprotective effect: Cyclosporine A is a potent immunosuppressive agent to prevent rejection of transplanted organs and treatment of autoimmune disease but its use is limited by nephrotoxicity (Myers, 1986). There are evidences that cGMP has an important role in protection of impaired renal function caused by cyclosporin through different mechanisms such as maintaining homeostasis in the kidney of the patients treated with cyclosporin A (Hosogai et al., 2001) and by increasing antioxidant protein levels that attenuates cyclosporin A toxicity (Polte et al., 2002) because cyclosporin increases free radical formation and it is considered to be important for its pathogenesis (Zhong et al., 1998). In addition, lowering Ca²⁺ concentration in cells protect them against the contraction and necrosis in vascular smooth muscle (Ruth, 1999; Pere et al., 1998). Thus, PDE5 inhibitors and modulators of NO-cGMP pathway by increasing cGMP content are potential pharmacological targets for protection against nephrotoxicity of cyclosporine (Hosogai et al., 2003).

Gastric mucosal protective effect: NSAIDs damage gastric mucosa via several mechanisms. By alteration blood flow in the mcosa, reducing synthesis of mucus and bicarbonate and decreasing mucosal cell proliferation (Scarpignato, 1995). These drugs also decrease NO synthesis (Kwon et al., 1997) while NO plays an important role in the protection of mucosa through cGMP (Tripp and Tepperman, 1995; Lopez-Belmonte et al., 1993). So PDE5 inhibitors have preventive effect against NSAIDs-induced gastropathy by inhibiting cGMP catalysis (Herreras et al., 2003).

Anti inflammatory effects: Brucella melitensis is a gram-negative facultative intracellular pathogen causing lipid peroxidation, decreasing activity of the antioxidant defence system, secreting inflammatory cytokines and suppressing PDE4A transcription during the infection with it (Erdogan et al., 2008; Melek et al., 2008). It has shown that cAMP a key intracellular second messenger has anti inflammatory and tissue protective effect in high intracellular level (Houslay and Adams, 2003). So, PDE4 inhibitors like rolipram can suppress these inflammatory responses by activating cAMP/PKA pathways and decreasing lipid peroxidation (Erdogan et al., 2007). This effect can be explained by this reason that PDE4 is the predominant isozyme of PDEs responsible for hydrolyzing cAMP in inflammatory and immune competent cells (Lynch et al., 2006).

Research by Toward and Broadley (2002) showed that chronic exposure to lipopolysaccharide as a model of COPD causes persistent broncho constriction, neutrophilic airway inflammation, goblet cell hyperplasia and edema. According to this article and other studies, PDE4 inhibition and elevation of cAMP level induce airway smooth muscle relaxation, alleviate inflammatory edema, suppress immune competent cell activation and migration (Sekut et al., 1995; Toward and Broadley, 2002).

Antioxidant effect: Organophosphorus compounds such as malathion and diazinon are effective insecticides and pesticides that are widely used in agricultural and medical practice. One of the mechanisms that proposed for their toxicity is induction of oxidative stress through the generation of Reactive Oxygen Species (ROS) (Milatovic et al., 2006) and inhibition of antioxidant enzymes in brain (Trevisan et al., 2008), blood, liver (Akhgari et al., 2003; Teimouri et al., 2006) and muscle (Amirkabirian et al., 2007). Based on recent studies PDE 5 inhibitors alone and in combination with theophylline possess antioxidant effects by increasing cellular cyclic nucleotides (Radfar et al., 2005; Abdollahi et al., 2003a).
Moreover, PDE 5 inhibitors can be helpful in treatment of toxicities caused by lead acetate, cadmium and can have beneficial role in diseases like Inflammatory Bowel Disease (IBD) and diabetes mellitus. Lead acetate can cause toxic effects in submandibular glands and liver through induction of lipid peroxidation while increasing intracellular cAMP and cGMP by PDEIs may play protective (Abdollahi et al., 2003b; Aghababaeian et al., 2005). Cadmium can inhibit submandibular gland function and secretion of proteins, enzymes and electrolytes (Abdollahi et al., 2000). Oxidative stress has been proposed as the main mechanism of its toxicity so that cAMP and cGMP PDEI can protect against this toxicity (Abdollahi et al., 2003a). Oxidative stress plays a pathogenic role in IBD and chronic complications of diabetes mellitus. Based on recent studies cAMP and cGMP PDEIs can maintain health in diabetes and PDEI 5 such as sildenafil is helpful in the management of IBD because of their antioxidant effect (Milani et al., 2005; Khoshakhlagh et al., 2007). Interestingly, recent studies indicated protective effects of PDEIs 3,4,5 in Langerhans islets from oxidative stress in vitro (Mohammadi et al., 2011).

DISCUSSION

In this study, we collected and reviewed the studies about the application of PDE inhibitors in treatment and prevention of toxicities. It is indicated that these drugs have therapeutic effects on some toxicities. Besides, they can protect against adverse effects of some drugs. PDE inhibitors may help consumption of the drugs of which their utilities have been limited owing to their adverse effects. Saiko et al. (1995) showed that the efficacy of amrinon is greater than epinephrine in treatment of bupivacaine-induced cardiovascular depression and along with the article of Lindgren et al. (1992) amrinon is superior to other pharmacological therapies for recovery of bupivacaine intoxication. Some studies showed that amrinon and milrinon as PDE3 inhibitors are effective agents in drug-induced heart failure and due to their positive inotropic activity, they are candidates for clinical testing in patient with congestive heart failure (Alousi et al., 1983, 1985; Sato et al., 1994). Moreover, PDE5 inhibitors have beneficial effects in preventing cardiotoxicity of doxorubicine, in that way they may expand therapeutic window of doxorubicin (Fisher et al., 2005; Koka et al., 2010). Therefore, PDE 3 and 5 inhibitors are the main types of this enzyme have protective role in cardiotoxicity. Furthermore, based on studies in this review, PDE 3, 4, 5 inhibitors have neuroprotective function and beneficial effects in treatment of toxicities caused by shiga toxin (Ookayama et al., 2004), malathion (Rezvanfar et al., 2010), MPTP (Hulley et al., 1995; Yang et al., 2008), quinolinic acid (DeMarch et al., 2007) and MDMA (Puerta et al., 2009). Anti inflammatory effect of PDE4 inhibitors makes them helpful in treatment of airway diseases and protection against Brucella melitiensis infection (Erdogan et al., 2008; Toward and Broadley, 2002; Holbrook et al., 1996; Kaneko et al., 2007). In toxicity of d-tubocurarine theophylline as a PDE1 and other cAMP level elevating agents have valuable role, because cAMP can promote neuromuscular transmission by facilitating the release of acetylcholine from motor nerve ending (Anttila and Vapaatalo, 1972). Antioxidant activity of PDE5 inhibitors make them helpful for protection against oxidative stress has been caused by organophosphorus compounds (Amirkabirian et al., 2007; Ghafor-Rashidi et al., 2007; Ranjbar et al., 2010; Azadbar et al., 2009) and in combination with cAMP PDE inhibitors can be useful in treatment of toxicities caused by lead acetate, cadmium and they also have beneficial role in diseases like Inflammatory Bowel Disease (IBD) and diabetes mellitus (Milani et al., 2005; Abdollahi et al., 2003a, b; Aghababaeian et al., 2005; Khoshakhlagh et al., 2007). Hepatoprotective outcome was observed with PDE4 and PDE5 inhibitors because of their anti-inflammatory effect (Matsushima et al., 2005;
Abdel-Salam et al., 2007). PDE5 inhibitors can ameliorate toxic effects included nephrotoxicity and gastric mucosal damage caused by cyclosporine and NSAIDs, respectively through increasing the content of intracellular cGMP (Hosogai et al., 2003; Herreras et al., 2003; Karakaya et al., 2009). Frye and Rhodes (2003) illustrated that PDE5 inhibitors can overcome SSRI-induced deficits in sexual function.

Although screening the applications of PDE inhibitors may help to find effective pharmacological therapies, they may have some adverse effects which can limit their usage. Consequently, it must be evaluated whether the advantages overcome their disadvantages. PDE enzymes have wide expression in the body and there are 11 families of this enzyme but based on this paper only inhibitors of 3 families (PDE 3, 4, 5) have protective role in toxicities. Therefore, it will be needed to investigate the application of inhibitors of other families in different toxicities in future. The studies discussed in this paper are mainly in vivo and for more reasonable and conclusive results, it is required to conduct human and clinical tests.

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