aJava

Asian Journal of Animal and Veterinary Advances

Academic
Journals Inc.

www.academicjournals.com

Asian Journal of Animal and Veterinary Advances 7 (3): 210-224, 2012
ISSN 1683-9919 / DOI: 10.3923/ajava.2012.210.224

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

[1,2]Sima Ghiasi, [3]Sindokht Ghiasi and [1,2]Mohammad Abdollahi

[1]Department of Toxicology and Pharmacology, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

[2]Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran, Iran

[3]Faculty of Veterinary Medicine, Urmia University, Urmia, Iran

Corresponding Author: Mohammad Abdollahi, Faculty of Pharmacy and Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran, Iran

ABSTRACT

Phosphodiesterase (PDE) enzymes are presented in nearly all cells and inhibitors of these enzymes have various pharmacological properties including cardiotonic, 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 mocusal damage and their beneficial role in inflammatory bowel disease and diabetes melitus. 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 (Ghosh *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 cylase, 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, PDE6, 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; Amsallem *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 toxicities 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 amrinon and milrinon 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 mocusa 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 mocusal damage, inflammation and oxidative stress.

Cardioprotective effect: Bupivacaine causes cardiovascular toxicity by alteration of Ca^{2+} release from cardiac sarcoplasmic reticulum (Lynch, 1986; Coyle and Sperelakis, 1987) and blockade of cardiac sodium channel (Clarkson and Hondeghem, 1985). Amrinon by inhibition of PDE3 in heart muscle increases intracellular cAMP thereby facilitates slow Ca^{2+} 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 amrinon is superior to epinephrin 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).

Table 1: Beneficial roles of PDEI 3,4,5 in different toxicities

Reference	Tissue	Study	Toxin	Effect	Drug	PDE type
Lindgren *et al*. (1992)	Heart	*In vivo* pig	Bupivacaine (19±5 mg kg^{-1})	Recovery from bupivacain intoxication	Amrinon (4 mg kg^{-1} bolus, followed by 0.6 mg/kg/min)	3 cAMP
Saitoh *et al*. (1995)	Heart	*In vivo* dog	Bupivacaine (0.5 mg/kg/min with infusion rate 0.5%)	Reversing bupivacaine-induced cardiovascular depression	Amrinon (4 mg kg^{-1} bolus followed by 0.1 mg/kg/min)	3 cAMP
Sato *et al*. (1994)	Heart	*In vivo*	Propranolol (10 mg kg^{-1})	Treatment of β-blocker poisoning	Milrinon (300μg kg^{-1})	cAMP
Alousi *et al*. (1985)	Heart	*In vivo* dog	Propranolol, Verapamil, Procainamide, Sodium pentobarbital	Treatment of acute drug induced heart failure	Amrinon (1 or 3 mg/kg bolus 0.03 or 0.1 mg/kg/min infusion)	cAMP
Alousi *et al*. (1983)	Heart	*In vivo* dog	Propranolol (4 mg/kg bolus+ 0.125-0.25 mg/kg/min infusion) Verapamil (100 μg/kg/min) Pentobarbital (5 or 10 mg kg^{-1})	Positive effect in reversing drug induced heart failure	Milrinon (bolus 30 μg kg^{-1}+ infusion 3 μg kg^{-1})	cAMP 3
Okayama *et al*. (2004)	Brain	*In vivo* mouse	Shiga toxin	Block brain damage by Shiga toxin	Rolipram, Pentoxyfyllin (7.5 mg kg^{-1})	3,4
Rezvanfar *et al*. (2010)	Rat blood and brain mithocondria	*In vivo* rat	Malathion (200 mg/kg/day)	Protection or recovery of Malathion toxic damage	Rolipram (200 μg/kg/day)	4 cAMP
Erdogan *et al*. (2008)	Plasma, Liver, Spleen	*In vivo* rat	Brucella melitensis (8×10^4)	Anti-inflamatory and tissue protective effect in infection	IBMX (1 mg kg^{-1})	4 cAMP
Holbrook *et al*. (1996)	Airway pathway	*In vitro* Isolated trachea, *In vivo* Gninea pig	Ozon (3.0± 0.5 ppm)	Inhibition of of bronchospasm and Ozon induced airway hyper responsiveness	CDP840 (1-10 μg kg^{-1} I.P)	4 cAMP
Hulley *et al*. (1995)	Substantia nigra neurons	*In vivo* Mouse	MPTP	Protection of dopaminergic neurons		4 cAMP
Yang *et al*. (2008)	Brain	*In vivo* Mouse	MPTP	Neuroprotective effect	Rolipram (1.25 or 2.5 mg kg^{-1})	4 cAMP
Matsuhashi *et al*. (2005)	Liver	*In vivo* rat	Thioacetamide (100 mg kg^{-1})	Hepatoprotective effect	Rolipram (0.5-5 mg kg^{-1})	4 cAMP
Anttila and Vapaatalo (1972)	Neuromuscular transmision	*In vivo* Mouse	d-Tubocurarin	↑LD50 value d-Tubocurarin	Theophylline	cAMP,cGMP
Kaneko *et al*. (2007)	Lung	*In vivo* Gninea pig	LPS of *E-coli* (30 μg mL^{-1})	Amelioration of chronic inflammatory airway disease	Theophylline	cAMP,cGMP

Table 1: Continued

Reference	Tissue	Study	Toxin	Effect	Drug	PDE type
DeMarch *et al*. (2007)	Striata spiny neurons	*In vivo* rat	Quinolinic acid (100 mM)	Therapeutic approach for HD disease	Rolipram (1.5 mg kg^{-1})	4 cAMP
Toward and Broadley (2010)	Airway pathway	*In vivo* Guinea pig	LPS of *E-coli* (30 μg mL^{-1})	Suppression of inflammatory processes of COPD	Rolipram (1 mg kg^{-1})	4 cAMP
Milani *et al* (2005)	Plasma	*In vivo* rat	Streptozotocin (45 mg kg^{-1})	Protection against oxidative stress in Streptozotocin induced diabetes	Milrinone (3.17 mg/kg/day), Sildenafil (1 mg/kg/day), Theophylline (100 mg/kg/day)	cAMP,cGMP
Ghafour-Rashidi *et al*. (2007)	Langerhans islets cells	*In vivo* rat	Diazinon (30 mg kg^{-1})	Restoration of Diazinon induced hyperglycemia and antioxidant effect	Theophylin(25 m kg^{-1}), Sildenafil (5 mg kg^{-1})	cAMP,cGMP
Abdollahi *et al*. (2003b)	Submandibular gland	*In vivo* rat	Lead acetate (100 mg kg^{-1})	Prevention of Lead-induced oxidative stress	Theophylline (25 mg kg^{-1}), Sildenafil (5 mg kg^{-1})	cAMP,cGMP
Abdollahi *et al*. (2003a)	Submandibular saliva	*In vivo* rat	Cadmium (10 mg kg^{-1})	Inhibiton of Cadmium -induced oxidative stress	Theophylline (25 mg kg^{-1}), Sildenafil (5 mg kg^{-1})	cAMPcGMP
Khoshakhlagh *et al*. (2007)	Colonic tissue	*In vivo* Mouse	Acetic acid	Management of IBD	Sildenafil (0.75, 1.5 and 3 mg kg^{-1})	5 cGMP
Aghababaeian *et al*. (2005)	Liver	*In vivo* rat	Lead 0.5 mM	Protection against Lead induced lipid peroxidation	Dipyridamole 50 M Sildenafil 50 M	5 cGMP
Ranjbar *et al*. (2010)	Brain mithocondria	*In vivo* rat	Malathion (200 mg/kg/day)	Protection against toxic stress and mithocondrial damage	Pentoxifylline (50mg/kg/ day)	5
Azadbar *et al*. (2009)	Brain mithocondria	*In vivo* rat	Malathion (200 mg/kg/day)	Protection against Malathion induced oxidative stress	Pentoxifylline (50 mg/kg/ day)	5
Amirkabirian *et al*. (2007)	Liver, mnscle	*In vivo* rat	Diazinon (60 mg/kg/day)	Alleviation of toxic stress by Diazinon	Pentoxifylline (100mg/kg/day)	5
Hosogai *et al*. (2003)	Kidney	*In vivo* rat	Cyclosporin (50 mg kg^{-1})	Amelioration of nephrotoxicity by Cyclosporin	FR226807 (10mg/kg)	5 cGMP
Puetra *et al*. (2009)	Serotonergic system in striatum	*In vivo* rat	MDMA (3×5 mg kg^{-1} every 2 h)	Protection against 5-HT depletion	Sildenafil (1.5 or 8 mg kg^{-1}), Vardenafil (1.5 mg kg^{-1})	5 cGMP
Herrerias *et al*. (2003)	Gasteric mocusa	*In vivo* rat	NSAIDs: ASA (100,300, 500 mg kg^{-1}), Piroxicam (5,10,20 mg kg^{-1}) Diclofenac Na (10,25,50,100 mg kg^{-1})	Protective effect on gasteric mocusa	Zaprinast (5 mg kg^{-1}), IBMX (10 mg kg^{-1})	5 cGMP

Table 1: Continued

Reference	Tissue	Study	Toxin	Effect	Drug	PDE type
Abdel-Salam *et al*. (2007)	Liver	*In vivo* rat	CCL_4 (1 mL/100 g weight)	Amelioration hepatic damage by CCL_4	Vinpocetin (4.8 mg kg^{-1})	cGMP
Karakaya *et al*. (2009)	Gastric mocusa	*In vivo* rat	Indomethacin (25 mg kg^{-1})	Protective effect on gasteric mocusa	Vardenafil (2 and 10 mg kg^{-1})	5 cGMP
Fisher *et al*. (2005)	Cardiomyocytes	*In vivo* male ICR mouse *In vitro* adult ventricular cardiomyocytes	Doxorubicin *In vivo* (5 mg kg^{-1}), *In vitro* (1 μmo L^{-1})	Cardioprotection from Doxorubicin-induced cardiotoxicity	Sildenafil *In vivo* (0.7 mg kg^{-1} I.P) *in vitro* (1 μmol L^{-1})	5 cGMP
Koka *et al*. (2010)	Heart	*In vivo* Mouse	Doxorubicin (15 mg kg^{-1} I.P single dose)	Cardioprotection	Tadalafil (4 mg kg^{-}1 po daily)	5 cGMP
Frye and Rhodes (2003)	Lateral displacement response	*In vivo* Hamster	Fluoxetin (10 mg/kg I.P)	Overcoming deficit sexual function by Fluoxetin	Zaprinast (3mg/kg I.P)	5 cGMP
Mohammadi *et al*. (2011)	Langerhans islet	*In vitro* rat	Reactive oxygen species	Increasing survival and function of islets	Milrinon, Rolipram, Sildenafil (0.01, 0.1, 1 μM)	3,4,5

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 micro angiopathy that results from the synergistic action of this toxin and pro inflammatory cytokines (tumor necrosis factor and interleukin1β) (Matussek *et al*., 2003; Paton and Paton, 1998; Obrig, 1997). PDEIs reduce production of proinflammatory cytokines (Essayan, 2001) and have 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-Methylenedioxymethamphetamine (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 (Commins *et al*., 1987). Puetra *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 (Matsuhashi *et al*., 2005). Matsuhashi *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 (Ca^{2+}) channel activity and through a negative feedback limits Ca^{2+} influx into excitable cells (Wu, 2003). Some study showed that limiting Ca^{2+} 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 Ca^{2+} 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 gasteric mucosa via several mechanisms. By alteration blood flow in the mocusa, 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 (Herrerias *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.*, 2006). 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 lipopolysacharide 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. Saitoh *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 (Okayama *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 (Puetra *et al*., 2009). Anti inflammatory effect of PDE4 inhibitors makes them helpful in treatment of airway diseases and protection against *brucella melitensis* 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 PDEI 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; Ghafour-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 (Matsuhashi *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; Herrerias *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.

ACKNOWLEDGMENT

This study is the outcome of an in-house non-financially supported study. Authors have no conflict of interest.

REFERENCES

Abdel-Salam, O.M., F.H. Oraby and N.S. Hassan, 2007. Vinpocetine ameliorates acute hepatic damage caused by administration of carbon tetrachloride in rats. Acta Biol. Hung., 58: 411-419.

Abdollahi, M., A.R. Dehpour and P. Kazemian, 2000. Interaction of cadmium with nitric oxide in rat submandibulary gland function. Pharmacol. Res., 42: 591-597.

Abdollahi, M., A. Bahreini-Moghadam, B. Emami, F. Fooladian and K. Zafari, 2003a. Increasing intracellular cAMP and cGMP inhibits cadmium-induced oxidative stress in rat submandibular saliva. Comp. Biochem. Physiol. C. Toxicol. Pharmacol., 135: 331-336.

Abdollahi, M., F. Fooladian, B. Emami, K. Zafari and A. Bahreini-Moghadam, 2003b. Protection by sildenafil and theophylline of lead acetate-induced oxidative stress in rat submandibular gland and saliva. Hum. Exp. Toxicol., 22: 587-592.

Aghababaeian, R., M. Ghazi-Khansari, K. Abdi, F. Taghadosinejad and M. Abdollahi, 2005. Protective effects of sildenafil and dipyridamol from lead-induced lipid peroxidation in perfused rat liver. Int. J. Pharmacol., 1: 157-160.

Akhgari, M., M. Abdollahi, A. Kebryaeezadeh, R. Hosseini and O. Sabzevari, 2003. Biochemical evidence for free radical-induced lipid peroxidation as a mechanism for Subchronic toxicity of malathion in blood and liver of rats. Hum. Exp. Toxicol., 22: 205-211.

Alousi, A.A., J.M. Canter, M.J. Montenaro, D.J. Fort and R.A. Ferrari, 1983. Cardiotonic activity of milrinone, a new and potent cardiac bipyridine, on the normal and failing heart of experimental animals. J. Cardiovasc. Pharmacol., 5: 792-803.

Alousi, A.A., J.M. Canter and D.J. Fort, 1985. The beneficial effect of amrinone on acute drug-induced heart failure in the anaesthetised dog. Cardiovasc. Res., 19: 483-494.

Amirkabirian, N., F. Teimouri, H. Esmaily, A. Mohammadirad, A. Aliahmadi and M. Abdollahi, 2007. Protection by pentoxifylline of diazinon-induced toxic stress in rat liver and muscle. Toxicol. Mech. Methods, 17: 215-221.

Amsallem, E., C. Kasparian, G. Haddour, J.P. Boissel and P. Nony, 2005. Phosphodiesterase III inhibitors for heart failure. Cochrane Database Syst. Rev., 10.1002/14651858.CD002230.pub2

Anttila, P. and H. Vapaatalo, 1972. Decreased toxicity of d-tubocurarine after pretreatment with drugs elevating the intracellular level of c-AMP in mice. Naunyn-Schmiedeberg's Arch. Pharmacol., 273: 175-178.

Azadbar, M., A. Ranjbar, A. Hosseini-Tabatabaei, A. Golestani, M. Baeeri, M. Sharifzadeh and M. Abdollahi, 2009. Interaction of phosphodiesterase 5 inhibitor with malathion on rat brain mitochondrial-bound hexokinase activity. Pestic. Biochem. Physiol., 95: 121-125.

Beavo, J.A., M. Conti and R.J. Heaslip, 1994. Multiple cyclic nucleotide phosphodiesterases. Mol. Pharmacol., 46: 399-405.

Beshay, E., F. Croze and G.J. Prud'homme, 2001. The phosphodiesterase inhibitors pentoxifylline and rolipram suppress macrophage activation and nitric oxide production *in vitro* and *in vivo*. Clin. Immunol., 98: 272-279.

Boswell-Smith, V., D. Spina and C.P. Page, 2006. Phosphodiesterase inhibitors. Br. J. Pharmacol., 147: S252-S257.

Bristow, M.R., M.E. Billingham, J.W. Mason and J.R. Daniels, 1978. Clinical spectrum of anthracycline antibiotic cardiotoxicity. Cancer Treat. Rep., 62: 873-879.

Clarkson, C.W. and L.M. Hondeghem, 1985. Mechanism for bupivacaine depression of cardiac conduction: Fast block of sodium channels during the action potential with slow recovery from block during diastole. Anesthesiology, 62: 396-405.

Commins, D.L., G. Vosmer, R.M. Virus, W.L. Woolverton, C.R. Schuster and L.S. Seiden, 1987. Biochemical and histological evidence that methylenedioxymethylamphetamine (MDMA) is toxic to neurons in the rat brain. J. Pharmacol. Exp. Ther., 241: 338-345.

Coyle, D.E. and N. Sperelakis, 1987. Bupivacaine and lidocaine blockade of calcium-mediated slow action potentials in guinea pig ventricular muscle. JPET, 242: 1001-1005.

DeMarch, Z., C. Giampa, S. Patassini, A. Martorana, G. Bernardi and F.R. Fusco, 2007. Beneficial effects of rolipram in a quinolinic acid model of striatal excitotoxicity. Neurobiol. Dis., 25: 266-273.

DeWitt, C.R. and J.C. Waksman, 2004. Pharmacology, pathophysiology and management of calcium channel blocker and β-blocker toxicity. Toxicol. Rev., 23: 223-238.

Decker, K., 1990. Biologically active products of stimulated liver macrophages (Kupffer cells). Eur. J. Biochem., 192: 245-261.

Degerman, E., P. Belfrage, A.H. Newman, K.C. Rice and V.C. Manganiello, 1987. Purification of the putative hormone-sensitive cyclic AMP phosphodiesterase from rat adipose tissue using a derivative of cilostamide as a novel affinity ligand. J. Biol. Chem., 262: 5797-5807.

Dehmer, T., J. Lindenau, S. Haid, J. Dichgans and J.B. Schulz, 2000. Deficiency of inducible nitric oxide synthase protects against MPTP toxicity *in vivo*. J. Neurochem., 74: 2213-2216.

Dousa, T.P., 1999. Cyclic-3,-5,-nucleotide phosphodiesterase isozymes in cell biology and pathophysiology of the kidney. Kidney Int., 55: 29-62.

Erdogan, S., S. Celik, O. Aslantas, T. Kontas and S. Ocak, 2007. Elevated cAMP levels reverse *Brucella melitensis*-induced lipid peroxidation and stimulate IL-10 transcription in rats. Res. Vet. Sci., 82: 181-186.

Erdogan, S., O. Aslantas, S. Celik and E. Atik, 2008. The effects of increased cAMP content on inflammation, oxidative stress and PDE4 transcripts during *Brucella melitensis* infection. Res. Vet. Sci., 84: 18-25.

Essayan, D.M., 2001. Cyclic nucleotide phosphodiesterases. J. Allergy Clin. Immunol., 108: 671-680.

Fisher, P.W., F. Salloum, A. Das, H. Hyder and R.C. Kukreja, 2005. Phosphodiesterase-5 inhibition with sildenafil attenuates cardiomyocyte apoptosis and left ventricular dysfunction in a chronic model of doxorubicin cardiotoxicity. Circulation, 111: 1601-1610.

Folcik, V.A., T. Smith, S. O'Bryant, J.A. Kawczak and B. Zhu *et al.*, 1999. Treatment with BBB022A or rolipram stabilizes the blood-brain barrier in experimental autoimmune encephalomyelitis: An additional mechanism for the therapeutic effect of type IV phosphodiesterase inhibitors. J. Neuroimmunol., 97: 119-128.

Frye, C.A. and M.E. Rhodes, 2003. Zaprinast, a phosphodiesterase 5 inhibitor, overcomes sexual dysfunction produced by fluoxetine, a selective serotonin reuptake inhibitor in hamsters. Neuropsychopharmacology, 28: 310-316.

Ghafour-Rashidi, Z., E. Dermenaki-Farahani, A. Aliahmadi, H. Esmaily, A. Mohammadirad, S.N. Ostad and M. Abdollahi, 2007. Protection by cAMP and cGMP phosphodiesterase inhibitors of diazinon-induced hyperglycemia and oxidative/nitrosative stress in rat langerhans islets cells: Molecular evidence for involvement of non-cholinergic mechanisms. Pest. Biochem. Physiol., 87: 261-270.

Ghosh, R., O. Sawant, P. Ganpathy, S. Pitre and V.J. Kadam, 2009. Phosphodiesterase inhibitors: their role and implications. IJPTR, 1: 1148-1160.

Green, A.R., A.O. Mechan, J.M. Elliott, E. O'Shea and M.I. Colado, 2003. The pharmacology and clinical pharmacology of 3,4-methylene-dioxymethamphetamine (MDMA, ecstasy). Pharmacol. Rev., 55: 463-508.

Harrison, S.A., D.H. Reifsnyder, B. Gallis, G.C. Cadd and J.A. Beavo, 1986. Isolation and characterization of bovine cardiac muscle cGMP-inhibited phosphodiesterase: A receptor for new cardiotonic drugs. Mol. Pharmacol., 29: 506-514.

Herrerias, J.M., J.M. Esteban, A.M. Caballero-Plasencia, M. Valenzuela-Barranco and V. Motilva *et al.*, 2003. Preventive effect of zaprinast and 3-Isobutyl, 1-methylxanthine (phosphodiesterase inhibitors) on gastric injury induced by nonsteroidal antiinflammatory drugs in rats. Dig. Dis. Sci., 48: 986-991.

Holbrook, M., N. Gozzard, T. James, G. Higgs and B. Hughes, 1996. Inhibition of bronchospasm and ozone-induced airway hyperresponsiveness in the guinea-pig by CDP840, a novel phosphodiesterase type 4 inhibitor. Br. J. Pharmacol., 118: 1192-1200.

Hood, Jr., W.B., 1989. Controlled and uncontrolled studies of phosphodiesterases 3 inhibitors in contemporary cardiovascular medicine. Am. J. Cardiol., 63: A46-A53.

Hosogai, N., J. Seki and T. Goto, 2001. Reciprocal regulation of cyclic GMP content by cyclic GMP-phosphodiesterase and guanylate cyclase in SHR with CsA-induced nephrotoxicity. Br. J. Pharmacol., 134: 995-1002.

Hosogai, N., M. Tomita, K. Hamada, T. Ogawa, J. Hirosumi, T. Manda and S. Mutoh, 2003. Phosphodiesterase type 5 inhibition ameliorates nephrotoxicity induced by cyclosporin A in spontaneous hypertensive rats. Eur. J. Pharmacol., 477: 171-178.

Houslay, M.D. and D.R. Adams, 2003. PDE4 cAMP phosphodiesterases: Modular enzymes that orchestrate signaling cross-talk, desensitization and compartmentalization. Biochem. J., 370: 1-18.

Huang, Z., Y. Ducharme, D. Macdonald and A. Robichaud, 2001. The next generation of PDE4 inhibitors. Curr. Opin. Chem. Biol., 5: 432-438.

Hulley, P., J. Hartikka, S. Abdel'Al, P. Engels and H.R. Buerki *et al.*, 1995. Inhibitors of type IV phosphodiesterases reduce the toxicity of MPTP in substantia nigra neurons *in vivo*. Eur. J. Neurosci., 7: 2431-2440.

Ikebe, M. and S. Reardon, 1990. Phosphorylation of smooth muscle myosin light chain kinase by smooth muscle Ca^{2+}/calmodulin-dependent multifunctional protein kinase. J. Biol. Chem., 265: 8975-8978.

Jacob, C., C. Szilagyi, J.M. Allen, C. Bertrand and V. Lagente, 2004. Role of PDE4 in superoxide anion generation through p44/42MAPK regulation: A cAMP and a PKA-independent mechanism. Br. J. Pharmacol., 143: 257-268.

Jeon, Y.H., Y.S. Heo, C.M. Kim, Y.L. Hyun, T.G. Lee, S. Ro and J.M. Cho, 2005. Phosphodiesterase: Overview of protein structures, potential therapeutic applications and recent progress in drug development. Cell Mol. Life Sci., 62: 1198-1220.

Kaneko, Y., K. Takashima, N. Suzuki and K. Yamana, 2007. Effects of theophylline on chronic inflammatory lung injury induced by LPS exposure in guinea pigs. Allergol. Int., 56: 445-456.

Karakaya, K., V. Hanci, S. Bektas, M. Can and H.B. Ucan *et al.*, 2009. Mitigation of indomethacin-induced gastric mucosal lesions by a potent specific type 5 phosphodiesterase inhibitor. World J. Gastroenterol., 15: 5091-5096.

Khoshakhlagh, P., M. Bahrololoumi-Shapourabadi, A. Mohammadirad, L. Ashtaral-Nakhai, B. Minaie and M. Abdollahi, 2007. Beneficial effect of phosphodiesterase-5 inhibitor in experimental inflammatory bowel disease; molecular evidence for involvement of oxidative stress. Toxicol. Mech. Methods, 17: 281-288.

Koka, S., A. Das, S.G. Zhu, D. Durrant, L. Xi and R.C. Kukreja, 2010. Long-acting phosphodiesterase-5 inhibitor tadalafil attenuates doxorubicin-induced cardiomyopathy without interfering with chemotherapeutic effect. J. Pharmacol. Exp. Ther., 334: 1023-1030.

Kondo, N., S. Shibita, I. Kodama and K. Yamada, 1983. Electrical and mechanical effects of amrinone on isolated guinea pigs ventricular muscle. J. Cardiovasc. Pharmacol., 5: 903-912.

Kotera, J., K. Fujishige and K. Omori, 2000. Immunohistochemical localization of cGMP-binding cGMP-specific phosphodieterase (PDE 5) in rat tissues. J. Histochem. Cytochem., 48: 685-693.

Kotera, J., T. Sasaki and K. Omori, 2005. Recent progress in cyclic nucleotide phosphodiesterase research: Isozymes, function and inhibitors. Nihon. Yakurigaku. Zasshi., 126: 121-127.

Kwon, G., H. Jr. Hill, J.A. Corbette and M.L. Daniel, 1997. Effects of aspirin on nitric oxide formation and denovo protein synthesis by RIN% F cells and rat islets. Mol. Pharmacol., 52: 388-405.

Lad, P.M., B.J. Goldberg, P.A. Smiley and C.V. Olson, 1985. Receptor specific threshold effects of cyclic AMP are involved in the regulation of enzyme release and superoxide production from human neutrophils. Biochim. Biophys. Acta (BBA)., 846: 286-295.

Landon, E.J., R.J. Naukam and B.V. Rama-Sastry, 1986. Effects of calcium channel blocking agents on calcium and centrilobular necrosis in the liver of rats treated with hepatotoxic agents. Biochem. Pharmacol., 35: 697-705.

Lefrak, E.A., J. Pitha, S. Rosenheim and J.A. Gottlieb, 1973. A clinicopathologic analysis of adriamycin cardiotoxicity. Cancer., 32: 302-314.

Lindeman J.P., J. Bailey and A.M. Watanabe, 1983. Potential biochemical mechanisms for regulation of slow inward current: Theoretical basis for drug action. Am. Heart. J., 103: 746-756.

Lindgren, L., T. Randell, N. Suzuki, J. Kytta, A. Yli-Hankala and P.H. Rosenberg, 1992. The effect of Amrinon on recovery from severe bupivacaine intoxication in pigs Anesthesiology., 77: 309-315.

Lopez-Belmonte, J., B.J. Whittle and S. Moncada, 1993. The actions of nitricoxide donors in the prevention or induction of injury to the rat gastric mucosa. Br. J. Pharmacol., 108: 73-78.

Lugnier, C., 2006. Cyclic nucleotide phosphodiesterase (PDE) superfamily: A new target for the development of specific therapeutic agents. Pharmacol. Ther., 109: 366-398.

Lynch, C., 1986. Depression of myocardial contractility *in vitro* by bupivacaine, Etidocaine and lidocaine. Anesth. Analg., 65: 551-559.

Lynch, M.J., E.V. Hill and M.D. Houslay, 2006. Intracellular targeting of phosphodiesterase-4 underpins compartmentalized cAMP signaling. Curr. Topics. Dev. Biol., 75: 225-259.

Macphee, C.H., S.A. Harrison, S.A. and J.A. Beavo, 1986. Immunological identification of the major platelet low-Km cAMP phosphodiesterase: Probable target for anti-thrombotic agents. Proc. Natl. Acad. Sci. USA., 83: 6660-6663.

Matsuhashi, T., M. Otaka, M. Odashima, M. Jin and K. Komatsuk *et al*., 2005. Specific type IV phosphodiesterase inhibit or ameliorates thioacetamide-induced liver injury in rats. J. Gastroenterol. Hepatol., 20: 135-140.

Matussek, A., J. Lauber, A. Bergau, W. Hansen and M. Rohde *et al*., 2003. Molecular and functional analysis of Shiga toxin induced response patterns in human vascular endothelialcells. Blood, 102: 1323-1332.

Melek, I.M., S. Erdogan, S. Celik, O. Aslantas and T. Duman, 2006. Evaluation of oxidative stress and inflammation in long term Brucella mehtensis infection. Mol. Cell. Biochem., 293: 203-209.

Milani, E., S. Nikfar, R. Khorasani, M.J. Zamani and M. Abdollahi, 2005. Reduction of diabetes-induced oxidative stress by phosphodiestrase inhibitors in rats. Comparative Biochem. Physiol., 140 C: 251-255.

Milatovic, D., R.C. Gupta and M. Aschner, 2006. Anticholinesterase toxicity and oxidative stress. Sci. World. J., 28: 295-310.

Mohammadi, M., S. Atashpour, N. Pourkhalili, A. Nili-Ahmadabadi and M. Baeeri *et al*., 2011. Comparative improvement in function of isolated rat langerhans islets by various phosphodiesterase 3, 4 and 5 inhibitors. Asian J. Anim. Vet. Adv., 6: 1233-1240.

Muller, T., P. Engels and J.R. Fozard, 1996. Subtypes of the type4 cAMP phosphodiesterases: Structure, regulation and selective inhibition. Trends. Pharmacol. Sci., 17: 294-298.

Myers, B.D., 1986. Cyclosporine nephrotoxicity. Kidney Int., 30: 964-974.

Obrig, T.G., 1997. Shiga toxin mode of action in *E. coli* O157: H7 disease. Front. Biosci., 15: d635-d642.

Okayama, A., K. Mikasa, N. Matsui, N. Higashi, M. Miyamoto and E. Kita, 2004. An interventional approach to block brain damage caused by Shiga toxin-producing Escherichia coli infection, by use of a combination of phosphodiesterase inhibitors. J. Infec. Dis., 190: 2129-2136.

Paton, J.C. and A.W. Paton, 1998. Pathogenesis and diagnosis of shiga toxin-producing *Escherichia coli* infections. Clin. Microbiol. Rev., 11: 450-479.

Pere, A.K., L. Krogerus, E.M. Mervaala, J. Laakso and H. Karppanen *et al*., 1998. Detrimental effect of dietary sodium and beneficial effect of dietary magnesium on glomerular changes in cyclosporin-a treated spontaneously hypertensive rats. Nephrol. Dial. Transplantation, 13: 904-910.

Polte, T., A. Hemmerle, G. Berndt, N. Grosser, A. Abate and H. Schroder, 2002. Atrial natriuretic peptide reduces cyclosporin toxicity in renal cells: Role of cGMP and heme oxygenase-1. Free Radical Biol. Med., 32: 56-63.

Puetra, E., I. Hervias, B. Goni-Allo, B. Lasheras, J. Jordan and N. Aguirre, 2009. Phosphodiesterase 5 inhibitors prevent 3,4-methylenedioxymethamphetamine-induced 5-HT deficits in the rat. J. Neurochem., 108: 755-766.

Radfar, M., B. Larijani, M. Hadjibabaie, B. Rajabipour, A. Mojtahedi and M. Abdollahi, 2005. Effects of pentoxifylline on oxidative stress and levels of EGF and NO in blood of diabetic type-2 patients: A randomized, double-blind placebo-controlled clinical trial. Biomed. Pharmacother., 59: 302-306.

Rahimi, R., S. Ghiasi, H. Azimi, S. Fakhari and M. Abdollahi, 2010. A review of the herbal phosphodiesterase inhibitors: Future perspective of new drugs. Cytokine, 49: 123-129.

Ranjbar, A., M.H. Ghahremani, M. Sharifzadeh, A. Golestani, M. Ghazi-Khansari, M. Baeeri and M. Abdollahi, 2010. Protection by pentoxifylline of malathion-induced toxic stress and mitochondrial damage in rat brain. Hum. Exp. Toxicol., 29: 851-864.

Rezvanfar, M.A., M.A. Rezvanfar, A. Ranjbar, M. Baeeri, A. Mohammadirad and M. Abdollahi, 2010. Biochemical evidence on positive effects of rolipram a phosphodiesterase-4 inhibitor in malathion-induced toxic stress in rat blood and brain mitochondria. Pesticide Biochem. Physiol., 98: 135-143.

Romero, G., B. Lasheras, L. Sainz-Suberviola and E. Cenarruzabeitia, 1994. Protective effects of calcium channel blockers in carbon tetrachloride-induced liver toxicity. Life Sci., 55: 981-990.

Rotella, D.P., 2002. Phosphodiesterase 5 inhibitors: Current status and potential applications. Nat. Rev. Drug Discovery, 1: 674-682.

Ruth, P., 1999. Cyclic GMP-dependent protein kinases: Understanding *in vivo* functions by gene targeting. Pharmacol. Ther., 82: 355-372.

Saitoh, K., Y. Hirabayashi, R. Shimizu and H. Fukuda, 1995. Amrinon is superior to epinephrine in reversing bupivacaine-induced cardiovascular depression in sevoflurane-anesthetized dogs. Anesthesiology, 83: 127-133.

Sato, S., M.H. Tsuji, N. Okubo and H. Naito, 1994. Milrinone versus glucagon: Comparative hemodynamic effects in canine propranolol poisoning. J. Toxicol. Clin. Toxicol., 32: 277-289.

Scarpignato, C., 1995. Nonsteroidal anti-inflammatory drugs: How do they damage gastroduodenal mucosa? Digestive Dis., 13: 9-39.

Sekut, L., D. Yarnall, S.A. Stimpson, L.S. Noel and R. Bateman-Fite *et al*., 1995. Anti-inflammatory activity of phosphodiesterase (PDE)-IV inhibitors in acute and chronic models of inflammation. Clin. Exp. Immunol., 100: 126-132.

Sperelakis, N. and G.M. Wahler, 1988. Regulation of Ca^{2+} influx in myocardial cells by beta adrenergic receptors, cyclic nucleotides and phosphorylation. Mol. Cell. Biochem., 82: 19-28.

Steffan, J.S., A. Kazantsev, O. Spasic-Boskovic, M. Greenwald and Y.Z. Zhu *et al*., 2000. The Huntington's disease protein interacts with p53 and CREB binding protein and represses transcription. Proc. Nat. Acad. Sci., 97: 6763-6768.

Teimouri, F., N. Amirkabirian, H. Esmaily, A. Mohammadirad, A. Aliahmadi and M. Abdollahi, 2006. Alteration of hepatic cells glucose metabolism as a non-cholinergic detoxication mechanism in counteracting diazinon-induced oxidative stress. Hum. Exp. Toxicol., 25: 697-703.

Torphy, T.J., 1998. Phosphodiesterase isozymes: Molecular targets for novel antiasthma agents. Am. J. Respir. Crit. Care Med., 157: 351-370.

Toward, T.J. and K.J. Broadley, 2002. Goblet cell hyperplasia, airway function and leukocyte infiltration after chronic lipopolysaccharide exposure in conscious Guinea Pigs: Effects of Rolipram and Dexamethasone. J. Pharmacol. Exp. Ther., 302: 814-821.

Travadi, J.N. and S.K. Patole, 2003. Phosphodiesterase inhibitors for persistent pulmonary hypertension of the newborn: A review. Pediatr. Pulmonol., 36: 529-535.

Trevisan, R., M. Uliano-Silva, P. Pandolfo, J.L. Franco and P.S. Brocardo *et al.*, 2008. Antioxidant and acetylcholinesterase response to repeated malathion exposure in rat cerebral cortex and hippocampus. Basic Clin. Pharmacol. Toxicol., 102: 365-369.

Tripp, M.A. and B.L. Tepperman, 1995. Effect of nitric oxide on integrity, blood flow and cychc GMP levels in the rat gastric mucosa: Modulation by sialoadenectomy. Br. J. Pharmacol., 115: 344-348.

Uckert, S., A. Kuthe, C.G. Stief and U. Jonas, 2001. Phosphodiesterase isoenzymes as pharmacological targets in the treatment of male erectile dysfunction. World J. Urol., 19: 14-22.

Wu, D.C., P. Teismann, K. Tieu, M. Vila, V. Jackson-Lewis, H. Ischiropoulos and S. Przedborski, 2003. NADPH oxidase mediates oxidative stress in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine model of Parkinson's disease. Proc. Nat. Acad. Sci., 100: 6145-6150.

Wu, S.N., 2003. Large-conductance Ca^{2+}-activated K^{+}channels: physiological role and pharmacology. Curr. Med. Chem., 10: 649-661.

Yang, L., N.Y. Calingasan, B.J. Lorenzo and M.F. Beal, 2008. Attenuation of MPTP neurotoxicity by rolipram, a specific inhibitor of phosphodiesterase IV. Exp. Neurol., 211: 311-314.

Zhong, Z., G.E. Arteel, H.D. Connor, M. Yin and M.V. Frankenberg *et al.*, 1998. Cyclosporin A increases hypoxia and free radical production in rat kidneys: Prevention by dietary glycine. Am. J. Physiol., 275: F595-F604.