CHAPTER 1

Introduction
1. INTRODUCTION

Repeated short episodes of ischemia and reperfusion have been demonstrated to make myocardium transiently more resistant to the deleterious effects of prolonged ischemia (Moroko et al., 1971). This paradoxical form of myocardial adaptation has been termed as classic ischemic preconditioning (Murry et al., 1986). The protective effect of classic ischemic preconditioning is transient and wane off gradually within 1 to 3 hours in different species (Baxter and Ebrahim, 2002). The delayed phase of protection, occurring many hours later and lasting much longer time, has been termed as second window of protection (SWOP) (Bolli, 2000; Bolli et al., 2011). Many pharmacological agents have produced ischemic preconditioning-like cardioprotective effect (Schultz et al., 1996; Sharma and Singh, 1999; Wang et al., 2007) and it has been termed as ‘pharmacological preconditioning’ (Klein et al., 2000, Koji et al., 2003; Yellon and Downey, 2003; Peng et al., 2011).

Diabetes is one of the major risk factors for ischemic heart (Kannel and McGee, 1979, Abbott et al., 1988). In the diabetic patients, the mortality rate after myocardial ischemic events is almost double than that of non diabetic subjects (Abbott et al., 1988; Herlitz et al., 1996). While some studies have reported that the diabetic heart is protected by ischemic preconditioning (Liu et al., 1993; Tatsumi et al., 1998; Ravingerova et al., 2000; Thirunavukkarasu et al., 2007), other studies have reported that cardioprotective effect of ischemic preconditioning is attenuated in diabetic subjects (Tosaki et al., 1996; Kersten et al., 2000; Nieszner et al., 2002; del Valle et al., 2002; Ravingerova et al., 2010). The cardioprotective effect of ischemic preconditioning is also attenuated by hyperlipidaemia (Udeda et al., 1999; Kyriakides et al., 2002; Ungi et al., 2005; Giricz et al., 2006; Kocsis et al., 2010).
mechanism by which cardioprotective effect of ischemic preconditioning is lost in hyperlipidaemic animals and modulated by diabetes mellitus is yet to be explored.

Glycogen synthase kinase-3β (GSK-3β) is a serine/threonine kinase found in all eukaryotes (Woodgett, 1990). The activation of PI-3K/Akt and subsequent inhibition of GSK-3β is responsible for the cardioprotective effect of ischemic preconditioning (Tong et al., 2004; Gross et al., 2004). Moreover inhibition of GSK-3β produces cardioprotection, perhaps through inhibition of mitochondrial permeability transition pore (MPTP) (Juhaszova et al., 2004; Feng et al., 2005). GSK-3β activity is elevated during diabetes mellitus (Eldar-Finkelman et al., 1999; Henriksen et al., 2003). Moreover increased GSK-3β activity may cause glucose intolerance (Pearce et al., 2004) and inhibition of GSK-3β may improve glucose tolerance in diabetes mellitus (Cline et al., 2002). It has been reported that diabetes mellitus may activate GSK-3β perhaps by impairing its upstream pathways (Gross et al., 2007). The transgenic mice that overexpress GSK-3β are hyperlipidaemic (Pearce et al., 2004). Moreover hyperlipidaemia is reported to increase the activity of PPAR-α (Kewalramani et al., 2006) which is known to activate GSK-3β by inhibiting its phosphorylation (Li et al., 2007). Furthermore it has been documented that hyperlipidaemia may activate GSK-3β through activation of platelet activating factor (PAF) (Prescott et al., 1996; Tong et al., 2001).

Heat shock protein 72 (HSP 72) is noted to produce late phase of cardioprotection by ischemic preconditioning (Hutter et al., 1994; Williams and Benjamin, 2000; Latchman, 2001; Snoeckx et al., 2001). The expression of HSP 72 is diminished in diabetes mellitus (Bruce et al., 2003), hyperlipidaemia (Csont et al., 2002) and conditions leading to overexpression of GSK-3β (Chu et al., 1998). However,
pharmacological inhibition of GSK-3β is noted to increase the expression of HSP 72 (Bijur & Jope, 2000; Wang et al., 2003).