OVERVIEW

The type-2 diabetes mellitus (T2DM) is considered as a metabolic disorder with high prevalence among diabetic biome. The pathophysiology of T2DM involves dysfunction of several organs including brain, liver and pancreas (Uysal et al., 2005; Gürpınar et al., 2012). The pathogenesis of T2DM involves a progressive development of insulin resistance (IR) in several tissues (Jurysta et al., 2013; Bazotte et al., 2014). It has been well documented that there is impairment in the activation of the insulin receptor substrate/phopstidylionositol-3 kinase/Akt (IRS/PI3K/Akt) signaling pathway in IR (Benomar et al., 2006). This leads to the reduction of the translocation of the glucose transporter-4 (GLUT-4) from the cytosol to the cell surface in several tissues (Furtado et al., 2002; Watson et al., 2004; Leney and Tavaré, 2009). This ultimately results in the reduction of glucose utilization in these tissues. Further, mitochondrial dysfunction is now generally accepted as a consistent attribute in most of the tissues in T2DM condition (Petersen et al., 2003; Lowell and Shulman, 2005; Kim et al., 2008; Johannsen and Ravussin, 2009). Therefore, it is imperative to evaluate the underlying mitochondria-linked PI3K/Akt/GLUT-4 signaling in such tissues in T2DM condition.

Gamma amino butyric acid (GABA) exerts effect in peripheral as well as brain tissues (Ackermann et al., 2008; Tian et al., 2011; Soltani et al., 2011). Additional research reports the presence of bicuculline-sensitive GABA-A receptor ($GABA_AR$) in the peripheral tissues (Minuk et al., 1987). It has been reported that GABA, through $GABA_AR$ stimulation, promotes the depolarization of membrane potentials by opening the voltage-dependent calcium channel in different cells (Tian et al., 2004; Kanai et al., 2009). Bicuculline-sensitive $GABA_AR$ activation promotes insulin secretion from pancreatic beta-cells through intracellular calcium-dependent PI3K/Akt signaling pathway in type-1 diabetic condition (Tian et al., 2011; Soltani et al., 2011).

Although this is proposed to be beneficial in the management of type-1 diabetes, this could be detrimental in severity of loss in insulin sensitivity in conditions such as T2DM (Tahara et al., 2008; Garabadu and Krishnamurthy, 2013). In contrast, $GABA_AR$ stimulation attenuates peripheral insulin resistance probably through activation of the Ca^{2+}/PI3K/Akt signaling pathway in several insulin sensitive tissues including autoimmune T-cells and adrenal chromaffin cells (Tian et al., 2011; Tian et al., 2004; Kanai et al., 2009). Thus, it is essential to evaluate the role of bicuculline-sensitive $GABA_AR$ activity on the mitochondria-linked PI3K/Akt/GLUT-4 signaling in T2DM condition.

The neuropsychiatric complications of T2DM is well documented and it has been well suggested that post-traumatic stress disorder (PTSD), an anxiety disorder, constitutes second largest population in the T2DM biome (Farr et al., 2015; Farr et al., 2014; Rao et al., 2014). PTSD is well characterzed with several behavioral manifestations including depression, anxiety and cognitive dysfunction (Liberzon et al., 1999; Harvey et al., 2006). Further, PTSD exhibits neuroendocrinological disorders including hypothalamus-pituitary-adrenal cortex-axis dysfunction (Liberzon et al., 1999; Harvey et al., 2006). Recently, IR and mitochondrial dysfunction at tissue level has been reported in the pathophysiology of PTSD (Sakandelidze et al., 2011; Krishnamurthy et al., 2013; Garabadu et al., 2015). These observations draw an attention to investigate the mitochondria-linked PI3K/Akt/GLUT-4 signaling to further elaborate the pathophysiology of PTSD.

Metformin, a well known mitochondrial complex-I inhibitor, is commonly used to mitigate IR in the treatment of T2DM (Davidson and Peters, 1997). Preclinical and clinical studies suggest that metformin ameliorates mitochondria dysfunction, defects in insulin signaling pathway in diabetic condition (Pryor et al., 2000; Kumar and Dey, 2002; Yuan et al., 2003;

Sonntag et al., 2005; Kukidome et al., 2006; Chakraborty et al., 2011; Qiu et al., 2012). Sertraline is one of the two FDA approved drugs in the management of PTSD in the global market (Krishnamurthy et al., 2013). Clinical as well as preclinical studies report the therapeutic effectiveness of sertraline in the pharmacotherapy of PTSD (Panahi et al., 2011; Wilson et al., 2014; Zhang et al., 2015). Further, sertraline has also been reported to have anti-hyperglycemic activity against experimentally-induced diabetic animals (Erenmemisoglu et al., 1999; Khanam and Pillai, 2006; Mahmood et al., 2010). Based on these facts, metformin and sertraline have been chosen for pharmacological evaluation of mitochondria-linked PI3K/Akt/GLUT-4 signaling pathway in T2DM and PTSD respectively. Further, the combination of metformin and sertraline has been evaluated for mitochondria-linked PI3K/Akt/GLUT-4 signaling pathway in the co-occurring condition of T2DM and PTSD in the experimental animals.

WORKING HYPOTHESIS

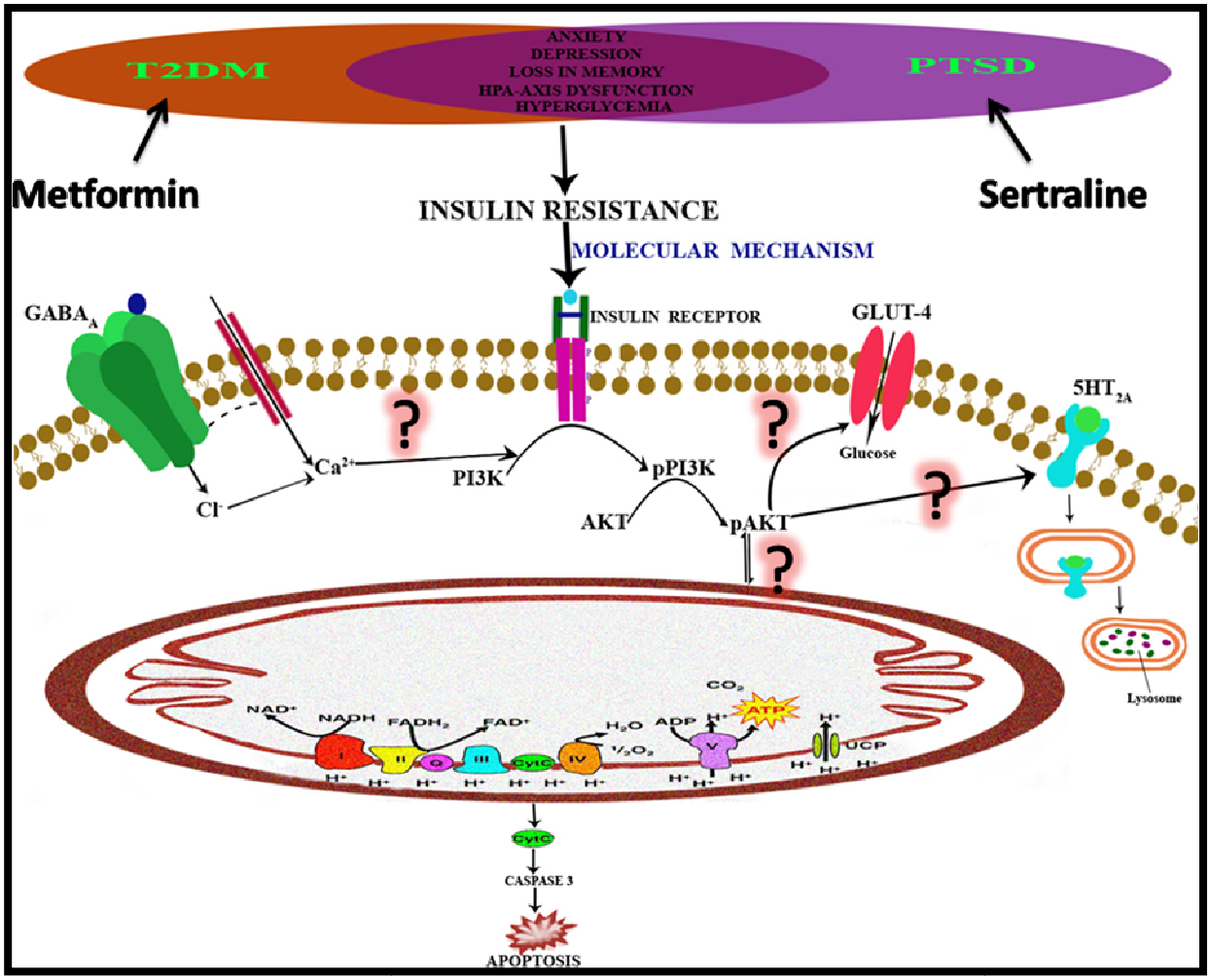

Figure 1: The schematic diagram of the working hypothesis for the present thesis work. Briefly, both type-2 diabetes mellitus (T2DM) and post-traumatic stress disorder (PTSD) share the common behavioral manifestations such as anxiety, depression and cognitive deficits, and endocrinological attributes like hypothalamus-pituitary-adrenal cortex (HPA-axis) function and insulin resistance. At sub-cellular level the work evaluates that how mitochondria function and phophatidylinositol-3-kinase (PI3K)/Akt-mediated GLUT-4 translocation signaling pathway interact with each other in such co-occurring condition. Further, an attempt has been made to evaluate the effect of bicuculline-sensitive $GABA_A$ and 5-HT_{2A} receptor activity on mitochondria-linked PI3K/Akt/GLUT-4 signaling in several tissues in such condition.

Objectives

- How metformin mediates mitochondrial-linked PI3K/Akt/GLUT-4 signaling in sub-chronic and chronic model of T2DM rats?
- What is the role of bicuculline-sensitive $GABA_A$ receptor on PI3K/Akt signalling pathway in T2DM rodents?
- What kind of effect metformin exerts on $GABA_A$-mediated PI3K/Akt pathway in T2DM rats?
- How sertraline manipulates the 5-HT receptor sub-types and mitochondria-linked PI3K/Akt/GLUT-4 signaling pathway in PTSD rats?
- Which could be the better option among metformin, sertraline and their combination for the co-occurring condition of T2DM and PTSD in experimental rats?