CHAPTER 2

AIMS AND OBJECTIVES

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RATIONALE OF THE STUDY

Insulin signaling is implicated in both central and peripheral mechanisms governing the overall body homeostasis. The role of insulin has been well defined in peripheral tissues in maintaining carbohydrate, protein and fat metabolism. However, involvement of insulin as a part of neural circuitry in maintaining the structure, metabolic activity and functions of brain has been investigated very lately. The cross talk of insulin signaling with neurotransmitters, neurotrophic factors, neuropeptides and neuro-hormones is instrumental in integration of peripheral and central cues to generate apt response. Nonetheless, the cellular, regional, functional as well as structural variations of insulin receptor in brain complicates the brain insulin signaling which is yet to be clearly understood. The recent explorations have uncovered a plethora of functions such as appetite regulation, cognition, energy balance, and so on, being regulated by brain insulin signaling, which makes it imperative to study the dysfunctions caused by brain insulin resistance as evident in many diseases.

Preclinical and clinical evidence supports a pathophysiological connection between altered metabolism, inflammation and insulin resistance in brain. Diseases such as diabetes, Alzheimer's, Parkinson's, and so on claims that there can be dysfunctions in the transport of insulin or insulin signaling or both in brain, a condition coined as "brain insulin resistance or Type 3 diabetes". Nowadays, burden of diabetes (type1 and type2 diabetes) is rising exponentially fuelled by the global increase in prevalence of obesity as well as unhealthy and stressful lifestyles. Several recent scientific breakthroughs have focused on correlations between diabetes and neurological disorders. Structural anomalies, physiological and psychological defects have been observed at CNS levels in patients suffering from diabetes. These negative effects have been attributed to hyperglycaemia, hyperinsulinemia, production of advanced glycation end products (AGEs) as well as reactive oxidation species (ROS) generation as a consequence of diabetes.

One of the key pathophysiological signature of Type 2 diabetes mellitus (T2DM) is hyperinsulinemia leading to peripheral insulin resistance. There are several reports supporting that peripheral insulin resistance can influence brain insulin signaling and cause derogatory effects. Likewise, the rodent models of obesity as well as diet induced

peripheral insulin resistance has demonstrated a decline in responsiveness to insulin in brain. Glucocorticoid (GC) is one of the common mediators of peripheral insulin resistance observed in obesity, stress as well as steroid induced diabetes. In peripheral insulin dependent tissues, corticosterone is known to develop insulin resistance leading to metabolic derangements. There are also striking similarities between neurological consequences in diabetes and chronic stress, thus further strengthening the hypothesis that GCs can be one of the culprit for brain insulin dysfunction along with peripheral insulin resistance. Thus, exploring the adverse effect of GCs using dexamethasone (a synthetic and more potent GC receptor agonist) induced diabetic model at regional, molecular and behavioral level can solve some of the missing links.

At cellular level, brain is composed of neurons as well as non-neuronal cells (or glial cells). The mesh of well-arranged inter dependent cellular network is mandatory for the proper brain functioning. Although neurons are known to be the functional units of brain, they are mostly post-mitotic. Thus, in any neuro degenerative diseases, the neuronal regeneration will mainly depend on astrocytes and neural stem cells (NSCs). Correspondingly, among different brain cells, astrocytes have been proved to be most insulin responsive and thus will be more susceptible to insulin resistance. Apart from being a supportive cell, astrocytic signals as well as its secretory factors are decisive in determining the fate of NSCs. Like astrocytes, NSCs are known to proliferate as well as differentiate in presence of insulin in concentration dependent manner. NSCs are also known to be affected in diabetic conditions where in rodent models reduced density of stem cells as well as decreased neurogenesis were prominent. However, it still remains to be established if the phenomenon of insulin resistance occurs in astrocytes or NSCs which might be one of the reason for reduced neuro regeneration or increased neuro degeneration. Also, as in peripheral insulin dependent cells where GC exposure can result into reduced insulin responsiveness, it would be interesting to known if similar phenomenon rests with astrocytes and NSCs.

This lead us to hypothesize that GC as well as GC mediated diabetes (especially peripheral insulin resistance) might result into impairment of the brain insulin signaling involving insulin resistance at cellular level in astrocytes and neural stem cells as schematically represented in Fig 2.1. Thus, *in vivo* and *in vitro* models of brain insulin resistance were established with the objective to co-relate glucocorticoid, peripheral insulin resistance and brain insulin resistance.

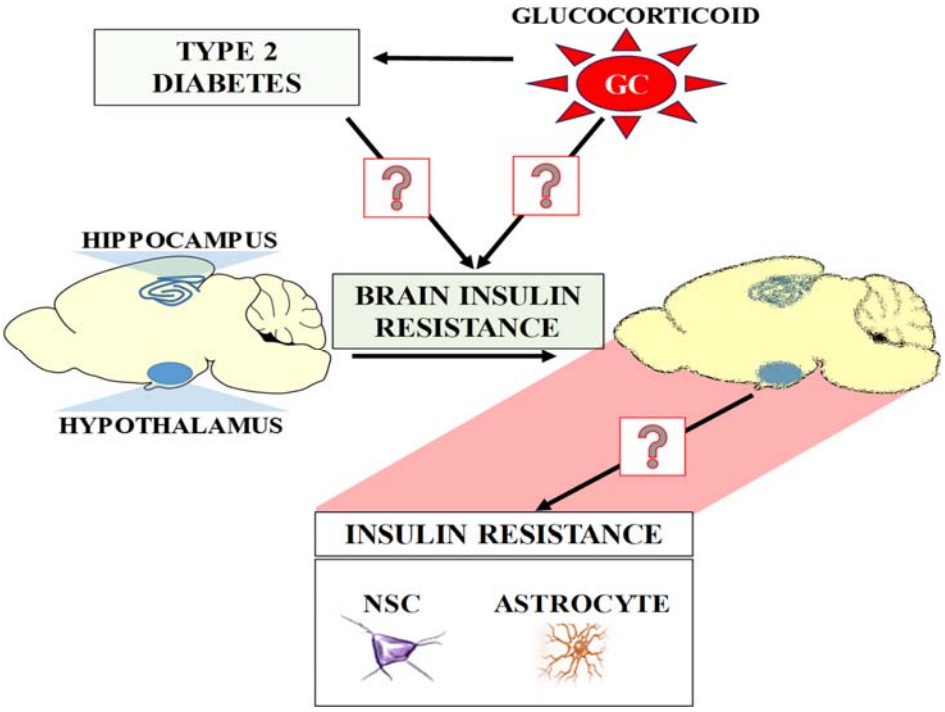

Figure 2. 1 Schematic representation of the hypothesis.

SPECIFIC OBJECTIVES

1] Regional and neurobehavioral study of brain insulin resistance in glucocorticoid induced diabetic rat model.

a) Assessment of region specific alterations in insulin signaling in glucocorticoid induced diabetic rat model and its correlation to neuro-behavior.

b) Impact of glucocorticoid induced maternal insulin resistance on hypothalamic appetite regulating circuitry of the neonatal brain.

2] To elucidate the role of insulin resistance and glucocorticoid on metabolism of astrocytes: An *in vitro* study.

a) Impact of insulin resistance on astrocyte metabolism.

b) Impact of glucocorticoid on insulin signaling of astrocytes.

3] To elucidate the role of insulin resistance and glucocorticoid on the fate of NSCs: An *in vitro* study.

a) Exploring the role of insulin in determination of NSC fate.

b) Impact of insulin resistance on NSCs.

c) Impact of glucocorticoid on insulin signaling in NSCs.