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Neuronal Insulin Signaling and Resistance: A Balancing Act of Kinases and Phosphatases and their Isoforms:

Insulin signaling is the principal pathway that regulates glucose homeostasis of the body. Insulin binds to insulin receptor and initiates a complex signaling cascade, leading to GLUT4 translocation and glucose uptake into the cells. Insulin-dependent tissues (Skeletal muscles, adipose tissue, and liver) are the chief modulators of effects of insulin on whole-body metabolism (Sharma & **Dey** 2021a). Post insulin stimulation, skeletal muscles stimulate glucose uptake (Abdul-Ghani & DeFronzo 2010), adipose tissue inhibit lipolysis (Kahn 2019) and liver suppresses glucose production (Adeva-Andany *et al.* 2016), working in tight conjugation in maintaining whole-body glucose metabolism. Any defects in this insulin signal transduction causes insulin resistance, which leads to various metabolic diseases. Amongst the top in metabolic diseases are Type-1, -2, -3 diabetes. Furthering the complication of metabolic diseases is the inevitability of peripheral insulin-dependent tissues to work in close conjunction with the brain.

Neuronal insulin signaling plays many important roles in the brain. Insulin signaling regulates neuronal apoptosis (Diez *et al.* 2012), neuronal survival, neurite outgrowth, synaptic plasticity (Levenga *et al.* 2017), release and uptake of catecholamine, expression of GABA, N-methyl-d-aspartate (NMDA) and α-amino-3-hydroxy-5- methyl-4-isoxazole propionic acid (AMPA) receptors trafficking of ligand-gated ion channels (Heide *et al.* 2003). Even after playing these diverse roles in brain, amongst the most important role in brain is in regulating neuronal glucose uptake (Gupta *…and* **Dey**. 2011; Gupta & **Dey** 2012). Neuronal insulin resistance is defined by inability of neurons to respond to insulin and mediate its effects. Physiologically, neuronal insulin resistance has been evidenced to contribute to improper central nutrient partitioning (Pardini *et al.* 2006), cognitive impairment (Perlmuter *et al.* 1984), neuropathology and neurodegeneration (Warby *et al.* 2009). There are several nodes in the neuronal insulin signaling cascade that have been identified as possible points of deregulation causing neuronal insulin resistance and related disorders. As in systemic insulin resistant conditions, hyperinsulinemia mediated neuronal insulin resistance is also characterized with downregulated insulin receptor affecting the entire signaling cascade till GLUT4 translocation and neuronal glucose uptake. Also neuronal insulin resistant diabetes has been linked to many neurodegenerative diseases like Alzheimer (Type-III diabetes) as observed by other laboratories and our own (de la Monte & Wands 2008; Gupta …and **Dey.** 2011), and including other diseases, like Huntington's disease (Humbert *et al.* 2002), spinocerebellar ataxia type 1 (Chen *et al.* 2003), schizophrenia (Emamian *et al.* 2004), Parkinson's disease (Furlong *et al.* 2019a) etc. Insulin signalling in insulin sensitive tissues are primarily regulated by a number of important kinases and phosphatases. In brain and neuronal insulin resistance also, there is no exception, and primarily regulated by a number of kinases and phosphatases. But in brain and neuron, the kinases and phosphatases, those are involved in the regulation of insulin signaling and insulin resistance, are relatively less known than skeletal muscle, adipocytes and hepatocytes. But they are known enough to consolidate them. However, there is no review in delineating kinases and phosphatases in regulating insulin signaling and insulin resistance. Therefore, in this review we attempt to consolidate key kinases and phosphatases, studies in our laboratory and others, in neuronal insulin signaling cascade. This consolidated article is expected to throw light in the current status of the signaling cascade, the balancing act of

kinases and phosphatases, the tight regulation necessary for normal neuronal insulin signaling and deregulation that contributes to neuronal insulin resistance.

(A) Kinase identified that are involved in insulin signaling and insulin resistance in neurons:

AKT kinase and its isoforms:

Akt is a Ser/Thr kinase that belongs to AGC family. This versatility of Akt is, in part, imparted by its isoforms. Akt has three isoforms: Akt1, Akt2 and Akt3 (Gonzalez & McGraw 2009). These isoforms are located at chromosomes 14q32, 19q13, and 1q44, respectively (Gonzalez & McGraw 2009). Interestingly, even though different genes on different chromosomes encode them, they have 80% sequence homology and share a common domain structure, with an N-terminal PH domain, a central kinase domain, and a C-terminal regulatory domain (Gonzalez & McGraw 2009). In insulin signaling and glucose uptake, paradoxical data about the three Akt isoforms has surfaced. Some studies negate role of Akt1 does in glucose metabolism (Noda *et al.* 2000; Chen *et al.* 2001; Cho *et al.* 2001; Cleasby *et al.* 2007). However, there are some studies that report Akt1 may play a role in insulin signaling and glucose uptake (Chen *et al.* 2009), reporting redundancy of Akt1 and Akt2 (Jiang *et al.* 2003; Kajno *et al.* 2015). Out of the three Akt isoforms, Akt3 was not studied in terms of glucose uptake with a primary role in brain (Dummler *et al.* 2006). All three Akt isoforms are expressed in the brain (Levenga *et al.* 2017; Gabbouj *et al.* 2019a, b). While the hippocampus expresses Akt1 and Akt3, astrocytes express Akt2 (Tschopp *et al.* 2005; Levenga *et al.* 2017; Gabbouj *et al.* 2019b). Gabbouj *et al.* (2019) reported that in mice hippocampus, insulin stimulation specifically increased Akt2 serine phosphorylation. However, Akt1 serine phosphorylation was not affected in the same study. Similarly, we have reported that all Akt isoforms are expressed in N2A and HT22 cells and were activated by phosphorylation almost ten-fold as a function of insulin stimulation (Sharma & **Dey** 2021b). Interestingly, they also reported that all Akt isoforms regulated glucose uptake, with Akt2 contributing the most, followed by Akt3 and Akt1, under insulin sensitive as well as resistant condition. Tschopp *et al.* (2005) had reported that Akt3 knock-out mice had smaller brain size and weight, without affecting whole-body glucose uptake. While we studied Akt isoform specific knockdown in neuronal cultures and testing neuronal glucose uptake, Tschopp *et al.* (2005) studied role of Akt3 specific whole-body knockout on whole-body glucose uptake. Akt isoforms have also been studied under neuronal insulin resistant conditions. We have reported that under hyperinsulinemia mediated insulin resistant condition, differential decrease in phosphorylation of all Akt isoforms in insulin-resistant neuronal cells post insulin stimulation happens. Akt2 phosphorylation was affected most, followed by Akt3 and Akt1 (Sharma & **Dey** 2021b). This was attributed to impaired translocation of Akt isoforms to plasma membrane under high-fat-diet or hyperinsulinemia mediated insulin resistant neuronal cells. Previously some studies have reported role of Akt isoforms in neurodegenerative diseases as well. Gabbouj et al (2019) reported that in the hippocampus of WT, but not APP/PS1 Alzheimer mice, phosphorylation of Akt2 was severely affected. Similarly, Wang et al (2015) has also reported contribution of all Akt isoforms to Alzheimer's disease. They reported that in cortical and cerebellar samples in mice brain, conditional knockout of all Akt isoforms affected Tau phosphorylation, a hallmark of Alzheimer's disease. Therefore, Akt isoforms play complex and differential roles in neuronal insulin signaling and resistance. Further studies are required to explore their complexity in insulin signaling and -resistance, paving way for possible therapeutic interventions.

AMP activated protein kinase (AMPK):

AMP activated protein kinase (AMPK) is known to be an energy sensor kinase (Hardie et al., 2012). AMPK is a heteromeric complex containing 3 subunits, AMPKα, AMPKβ and AMPKγ (Entezari et al., 2022). The α subunit of AMPK contains a kinase domain, an autoinhibitory domain (AID) and a C-terminal domain (CTD). The AID is responsible for the inhibition of AMPK in absence of AMP and CTD contains serine residues and phosphorylation at serine 485/491 inhibits the activity of AMPK. α subunit of AMPK also contains catalytic domain where phosphorylation at Thr172 residue causes the activation of AMPK (Stein et al., 2000). AMPK is reported to be activated in response to insulin (Bertrand et al., 2006). In insulin responsive tissue like skeletal muscle, liver and adipocytes studies reported the importance of AMPK in promoting the translocation of GLUT4 hence increasing the uptake of glucose (Entezari et al., 2022). AMPK is highly expressed in brain (Culmsee *et al.* 2001) and regulates various cellular processes like energy homeostasis and food intake (Claret *et al*., 2007). AMPK is known to be a neuroprotective under pathological conditions which when activated in neurons, prevents the development of neurodegenerative disorders, like Alzheimer's Disease (AD) (Vingtdeux *et al.* 2010). Since glucose is the primary energy source of brain and neurons are reported to be very sensitive to energy fluctuations, AMPK being very well-known energy sensor molecule sought to be a key player for sensing and utilizing the glucose inside the neurons. Studies from our laboratory reported the role of AMPK in neuronal insulin signaling. We have demonstrated the positive role of AMPK in neuronal glucose uptake (Patel…and **Dey.** 2011). When neuronal cell lines were treated with AMPK activator, 5-Aminoimidazole-4-carboxamide ribonucleotide (AICAR), increase in phosphorylation of Thr172 residue of AMPK at catalytic subunit, meaning its activation, was observed. AICAR treated cell showed enhanced neuronal glucose uptake suggesting AMPK promoting neuronal glucose uptake. The use of Compound C in neuronal cells antagonize the effect of AICAR confirming the positive role of AMPK in regulating neuronal insulin signaling and insulin resistance (Patel…and **Dey.** 2011). Interestingly, another study from our laboratory demonstrated regulation occurred through a PPM family of Ser/Thr phosphatase PP2Cα (Yadav & **Dey** 2022a). The study demonstrated that PP2Cα acts on Thr172 residue of AMPK catalytic site, inactivating it and hence regulating the neuronal glucose uptake under insulin sensitive and insulin resistant conditions positively. It is interesting to note that these two studies established the contrasting role of AMPK in neuronal insulin signaling and insulin resistance, providing the evidence of complicated regulations of a kinase in the same cascade. Such regulations (especially in this case) were coming through a phosphatase (PP2Cα) establishing the fact that phosphatases along with the kinases are important players of neuronal insulin signaling. Inhibition or activation of either AMPK or PP2Cα may shift this equilibrium and direct the uptake of neuronal glucose in either direction. Such a balance of both AMPK and PP2Cα might be utilized in future to improve neuronal insulin resistance and overcoming AD pathogenesis.

Focal adhesion kinase (FAK):

Focal adhesion kinase (FAK) is non receptor tyrosine kinase. FAK consists of 4 domains, namely, FEM domain, linker domain, kinase domain and focal adhesion targeting (FAT) domain. All these domains contain phosphorylation sites at histidine and tyrosine residues required for the activation. We and Huang's group have identified the role of FAK in insulin signaling in peripheral tissues as well as in neurons (Huang *et al.* 2002, 2006; Bisht *et al.* 2007, 2008; Bisht & Dey 2008; Gupta & Dey 2009). Our laboratory and some other studies

established very interesting and contrasting roles of FAK in insulin signaling and insulin resistance. FAK in hepatocytes and skeletal muscles positively regulates glycogen synthesis (Huang *et al.* 2002, 2006). This positive role of FAK has also been observed in adipocytes, where study demonstrated that FAK positively regulates glucose uptake (Müller *et al.* 2000). However, the activity of FAK (as determined by Tyr phosphorylation), was found to be reduced under insulin resistant condition in C2C12 muscle cells (Bisht *et al.* 2007), liver (Cheung *et al.* 2000) and high-fat-fed-diet (HFD) mice (Bisht *et al.* 2007). This confirmed that in peripheral tissues like skeletal muscle, adipocytes and hepatocytes, FAK is a positive regulator of insulin signaling. The role of FAK in neuronal insulin signaling was in sharp contrast with other peripheral tissues. Interestingly, *in vitro* insulin resistant model from our laboratory revealed FAK to be a negative regulator of neuronal insulin signaling and its activity was increased under insulin resistant condition (Gupta….& **Dey.** 2012). Downregulation of FAK enhanced the translocation of insulin-dependent glucose transporter GLUT4 from cytoplasm to membrane leading to increase in neuronal glucose uptake (Gupta….& **Dey.**2012). FAK in neuronal system followed the classical insulin signaling pathway as established so far i.e., phosphorylation mediated activation of insulin receptor (IR) to IRS-1 to PI3K to Akt to GLUT4 translocation to glucose uptake (Gupta….& **Dey. *2***012). Such studies provided the insight that FAK has tissue specific role. One reason behind such tissue specific role of FAK was revealed through studies signifying that FAK expressing in neurons is very different than the FAK expressed in non-neuronal cells (Burgaya *et al.* 1997). FAK in neuronal cells is larger in size as compared to non-neuronal cells due to insertion of various splice variants. This mediates the autophosphorylation of FAK ensuring the tight regulation of insulin signaling (Burgaya *et al.* 1997; Toutant *et al.* 2002). Another reason of tissue specific role of FAK, what we have seen, could be due to phosphatase, phosphatase and tensin homolog (PTEN) (Gupta & Dey 2009). In neuronal cells this phosphatase has been seen to directly act on FAK, regulating its activity by dephosphorylating at Tyr residue (Gupta & **Dey** 2009). Such tissue specific regulation of a kinase in same signaling cascade provides a perception that insulin signaling cascade is a complex web and is under tight regulation with each and every kinase and phosphatase regulating it. Both phosphorylation and dephosphorylation events are important for such regulation where a kinase and phosphatase could change the regulation in a tissue specific manner. Further deciphering the role of FAK with reference to each kinase and phosphatase is important and will help to unentangle the web of insulin signaling in different tissues, especially in neurons.

Protein activated kinase 2 (PAK2):

Protein activated kinase 2 (PAK2) is a Ser/Thr kinase, known to regulate several cellular processes like proliferation, apoptosis, metastasis and cytoskeleton remodelling (Bokoch 2003; Rane & Minden 2014). Based on structural and biochemical properties, PAKs are divided into two groups: Group 1 which contains PAK1, PAK2 and PAK3 and Group II which contains PAK4 and PAK5. Structurally, PAK2 is composed of a regulatory domain containing, autoinhibitory domain (AID), catalytic domain and a p-21 binding domain (PBD). In an inactive state, AID interacts with catalytic domain causing the inhibition of its kinase's activity. As soon as GTP-bound Cdc42 disrupts the autoinhibition, it leads to PAK autophosphorylation at Ser sites leading to the activation. PAK3, PAK2 is ubiquitously expressed and to be found in rat neuroblast cells and known to be activated through various kinases (Roig & Traugh 2001). Apart from participating in various neurological disorders like Huntington's Disease (Tourette *et al.* 2014), schizophrenia (Carroll *et al.* 2011) and cerebral hemorrhage (Bright *et al.* 2009), we have reported PAK2 to be involved in neuronal insulin signaling cascade (Varshney & **Dey** 2016). The role of PAK2 in neuronal insulin signaling

contrasts with its role in other peripheral tissues. For example, in L6 skeletal muscle myoblasts and pancreatic acini, insulin was known to have no effect on expression and activation of PAK2 (Nuche-Berenguer & Jensen 2015). However, reports from our laboratory demonstrated the effect of insulin stimulation on activity of PAK2 in mouse neuroblastoma and hippocampal cells (Varshney & **Dey** 2016), indicating the possible role of PAK2 in neuronal insulin signaling. We have observed marked decrease in phosphorylation of PAK2 suggesting the decrease in activity of PAK2 post insulin stimulation. PAK2 downregulation enhanced the neuronal glucose uptake, however in contrast, its overexpression causes reduction in neuronal glucose uptake. These observations suggest the role of PAK2 as a negative regulator of neuronal insulin signaling (Varshney & **Dey** 2016). Few studies in fibroblasts (Hough *et al.* 2012), macrophages (Wang *et al.* 2011) and kidney (Wang *et al.* 2010) demonstrated that the activation of PAK was coming from PI3K and Akt being reported as both upstream (Sato *et al.* 2013) or downstream (Wang *et al.* 2010) to PAK2. Akt inhibitor Akti-1/2 and PI3K inhibitor wortmannin in N2a cells in our system confirmed the involvement of PI3K-Akt upstream of PAK2, regulating its activity in insulin sensitive and insulin resistant N2a cells (Varshney & **Dey** 2016). One of the mechanisms is involvement seems to be a Ser/Thr phosphatase, PP2A. In neutrophils PP2A is known to dephosphorylate PAK2 and regulate its activity (Zhang *et al.* 2013). We have seen when PP2A was inhibited by okadaic acid in N2a cells , it increased the activity of PAK2 resulting in decreased insulin stimulated glucose uptake without affecting the activity of Akt (Varshney & **Dey** 2016). The study proved the role of PAK2 in neuronal glucose uptake, which is independent of Akt regulation but regulated via PP2A. In our study inhibition of Rac1 showed decrease in PAK2 activity leading to increase in neuronal glucose uptake (Varshney & **Dey** 2016). Interestingly this Rac-1-dependent regulation of PAK2 was found to be insulin-independent. Overall, the study elucidated the role of PAK2 as a negative regulator of neuronal insulin signaling and insulin resistance. This is in contrast to other peripheral tissues (in insulin signaling) and adding a new kinase in insulin signaling cascade, at least in neuronal system. This study remarkably showed the involvement of one of the Ser/Thr phosphatase PP2A acting on PAK2 and regulating the translocation of GLUT4 affecting the neuronal glucose uptake. Along with the addition of a new kinase i.e., PAK2, interaction with a phosphatase, PP2A showing the importance of kinases and phosphatases in neuronal insulin signaling and insulin resistance.

(B) Phosphatases identified that are involved in insulin signaling and insulin resistance in neurons:

PHLPP:

Pleckstrin Homology (PH) domain Leucine-rich repeat Protein Phosphatases (PHLPP) is composed of N-terminal PH domain, Leucine-rich repeat (LRR) region, PP2C (protein phosphatase type 2C) phosphatase domain, and the C-terminal PDZ-binding motif (Gao *et al.* 2005). It belongs to protein phosphatase type 2C (PP2C) family of Ser/Thr phosphatases which are in turn a part of the protein phosphatase metal-dependent (PPM) family. The PHLPP phosphatases are composed of two isoforms: PHLPP1 (variants PHLPP1α and PHLPP1β) and a separate gene product, PHLPP2. Both the isoforms of PHLPP and the splice variants of PHLPP1 share the same domain composition (Gao *et al.* 2008). PHLPP regulates a myriad of signaling, like in neuronal survival (Boonying *et al.* 2019), neuroprotection (Chen *et al.* 2013), neuronal apoptosis (Wei *et al.* 2014), memory formation (Shimizu *et al.* 2007), long term memory consolidation (Shimizu *et al.* 2010), etc. Expression of PHLPP isoforms has been studied across several metabolic tissues, under normal and pathological conditions like obesity

and diabetes. In skeletal muscles biopsies of diabetic patients, Cozzone et al (2008) reported elevated mRNA expression of PHLPP1 but not PHLPP2. This in-turn affected serine phosphorylation of Akt2 and Akt3 but not Akt1. Andreozzi et al (2011) reported elevated PHLPP1expression in skeletal muscles and in abdominal subcutaneous adipose tissue samples of morbidly obese participants, with corresponding decrease in Akt serine phosphorylation. Increased abundance of only PHLPP1 and not PHLPP2, positively correlated with body mass index (BMI), fasting insulin levels and homeostatic model assessment (HOMA) index of insulin resistance. Interestingly, these studies negate any involvement of PHLPP2 under pathological disorders. Kim et al (2021) reported that in adipose tissue of obese leptin receptor-deficient db/db mice showed elevated PHLPP2 expression as well. Wu et al (2020) reported similar findings, elevated PHLPP2 expression regulated inter-organ cross-talk between adipose tissue and liver through exosome-derived miR-130a, and hepatic miR-130a thereby regulating glucose uptake. Kim et al (2017) reported that liver-specific PHLPP2 knockout as compared to C57BL/6J mice, obese db/db mice, under normal chow or high fat diet showed reported PHLPP2 knockout (KO) induced lipogenesis without affecting gluconeogenesis. This hepatic specific PHLPP2 KO increased Akt, eventually exacerbating non-alcoholic fatty liver disease (NAFLD). Hyperglycemia mediated pancreatic β cells reported increased PHLPP1 and PHLPP2 expression (Hribal *et al.* 2020). In human islets and β-cells under glucotoxic conditions *in vitro* and in islets from diabetic mouse models and in patients with type-2 (T2D) reported upregulated PHLPP1 and PHLPP2. Most recently, we have observed elevated expression of both PHLPP1 and PHLPP2 in insulin resistant neuronal cells (Neuro-2A, SH-SY5Y) as well as in the whole brain lysates of high-fat-diet mediated diabetic mice (Sharma and **Dey,** 2022). It was first reported that PHLPP1 specifically regulates Akt2 and Akt3, while PHLPP2 regulates Akt1 and Akt3 in H157, Hs578Bst and 293T cell lines (Brognard *et al.* 2007). Similarly, in human pancreatic ductal adenocarcinoma (PDAC) and normal pancreatic tissue samples *in vivo* as well as in PaCa-2 and PANC-1 cell line *in vitro* reported similar findings, that PHLPP1 regulates Akt2 and PHLPP2 regulates Akt1 specifically (Nitsche *et al.* 2012). In mice xenografts derived from PaCa cells, increased apoptosis was attributed to inactivated Akt2 and elevated PHLPP1. In contrast to these studies, post leukemia inhibitory factor stimulation in neonatal rat ventricular myocytes (NRVMs) and in adult mouse ventricular myocytes, PHLPP1 silencing cardiomyocytes, Miyamoto et al (2010) reported comparable increase in phosphorylation of Akt1 and Akt2, without any effect post PHLPP2 silencing. Another study in mice heart reported PHLPP1 KO increased Akt1 activity following transverse aortic constriction pressure (but not Akt2), increasing cardiomyocyte size and leading to pathological hypertrophy (Moc *et al.* 2015). In neuronal system, Chen et al (2013) reported PHLPP1 KO increased Akt activity, without any effect on Akt isoform expression. However, Akt isoform specific phosphorylation post PHLPP1 KO was not addressed in this study. We recently reported PHLPP1 regulates Akt2 and Akt3, while PHLPP2 regulates Akt1 and Akt3, in neuronal insulin signaling and resistant conditions (Sharma and **Dey,** 2022*)*. This PHLPP mediated Akt isoform specific regulation activated AS160 affecting glucose uptake. As explained earlier, Cozzone et al (2008) had attributed decreased Akt2 and -3 serine phosphorylation in skeletal muscles of T2D patients to increased PHLPP1 mRNA levels. Interestingly, we observed all Akt isoforms differentially regulated AS160, glucose uptake, and neuronal insulin resistance, wherein Akt2 contributed the most, followed by Akt3 and Akt1. We have also observed elevated expression of both PHLPP1 and PHLPP2 under neuronal insulin resistant conditions, which may be correlated to Akt isoform specificity . Previously, Xiong *et al* (2017) had reported both PHLPP isoforms regulated glucose uptake in SW480, DLD1 and Caco2 cells via Akt. However, PHLPP isoforms regulate Akt isoforms specifically, affecting AS160 and glucose uptake specifically has been reported for the first time in neuronal cells by us (Sharma and **Dey**, 2022). Thus, differential expression profile

across various tissues under normal and pathological conditions conveys the complexity and importance of PHLPP isoforms. Since many studies have established individual as well as over-lapping roles of PHLPP isoforms in disease states, further studies deciphering possible roles in other neurodegenerative diseases holds promise in the future.

PP2Cα:

PP2Cs belongs to Mg^{2+} or Mn^{2+} dependent (PPM) family of Ser/Thr phosphatase (McGowan & Cohen 1988). PP2Cα is one of the isoforms of PP2Cs and is extensively reported in regulating stress signaling (Lammers & Lavi 2007). PP2Cα contains C-terminal and N-terminal domain which determines the substrate specificity and catalytic domain required for Mg^{2+} and Mn^{2+} binding (Das *et al.* 1996). Other than stress signaling, PP2Cα in insulin signaling so far is very less reported. There is only one report which demonstrated the positive role of PP2Cα in insulin signaling in 3T3-L1 adipocytes (Yoshizaki *et al.* 2004). We have recently demonstrated the positive role of PP2Cα in neuronal insulin signaling (Yadav & **Dey** 2022a). Our study not only demonstrated the physiological importance of PP2Cα in regulating neuronal insulin signaling and insulin resistance, but also provided the first evidence of rapid translation of a phosphatase, PP2Cα, in response to insulin. Interestingly, we observed that this translation of PP2Cα was reduced under insulin resistance. We also observed JNK is the kinase mediating the translation of PP2Cα both under insulin sensitive and under insulin resistant condition (Yadav & **Dey** 2022a). Furthermore, it was found that neuronal glucose uptake was hampered when PP2Cα was diminished, suggesting a positive role of PP2Cα. The reason behind this regulation was dephosphorylating one of the inhibitory phosphorylation of IRS-1 at Ser522 (Yadav & **Dey** 2022a). This phosphorylation was reported to be inhibitory for insulin signaling (Giraud *et al.* 2007), but the role and regulation of insulin signaling through this phosphorylation has never been reported. We reported for the first time that under insulin sensitive condition PP2Cα keeps IRS-1 dephosphorylated at Ser522 residue, promoting insulin signaling. Oppositely, under insulin resistance condition IRS-1 was more phosphorylated at Ser522 residue and PP2Cα was less (due to less translation), hence reduction in neuronal glucose uptake was observed. Study by Kovacic *et. al.* 2003 reported that Akt negatively regulates the activity of AMPK in heart Also, it was reported that in hepatocytes and skeletal muscles, in response to insulin, AMPK was phosphorylated at Ser 485/491 by Akt causing the exposure of phosphorylation of AMPK at Thr172 residue in activation loop (Valentine *et al.* 2014). Thus, the exposure of this phosphorylation creates it as a target for different kinases and phosphatases. We observed that when PP2Cα was diminished under insulin sensitive condition, either through inhibition or downregulation, the phosphorylation of AMPK at Thr172 in the activation loop was increased. Under insulin resistant condition the phosphorylation of AMPK at Thr172 was further increased when PP2Cα was diminished (Yadav & **Dey** 2022a). The study demonstrated the regulation of neuronal insulin signaling through AMPK by regulating its phosphorylation through PP2Cα. So, PP2Cα is a positive regulator of neuronal insulin signaling and insulin resistance. A neuronal cell in response to insulin through JNK increases the expression of PP2Cα under insulin sensitive condition, while when insulin signaling is hampered i.e., under insulin resistance, the expression of PP2Cα was reduced. Due to the availability of PP2Cα (when PP2Cα is more expressed under insulin sensitive condition), it acts on the inhibitory Ser522 phosphorylation of IRS-1 and regulates the activity of AMPK by dephosphorylating at Thr172 and promotes insulin signaling. On the other hand, when PP2Cα was less (due to reduced expression under insulin resistant condition), the phosphorylation of IRS-1 at Ser522 and AMPK at Thr172 was more. This provided the evidence that neuronal cell requires PP2Cα to promote neuronal insulin signaling through IRS-1 and AMPK. One of our studies also linked PP2Cα with the progression of AD pathogenesis

(Yadav and **Dey,** 2022b). We found that the positive role of PP2Cα in neuronal insulin signaling also helps in the prevention of development of AD like phenotypes (Yadav and **Dey**, 2022b). Hence, we can, overall, say that PP2Cα regulates the cascade of neuronal insulin signaling in an interesting manner, where it promotes neuronal insulin signaling, prevents neuronal insulin resistance ultimately preventing AD like phenotypes. Future studies are necessary to consider the possibilities of PP2Cα and its regulation for possible therapeutic intervention.

PP1γ:

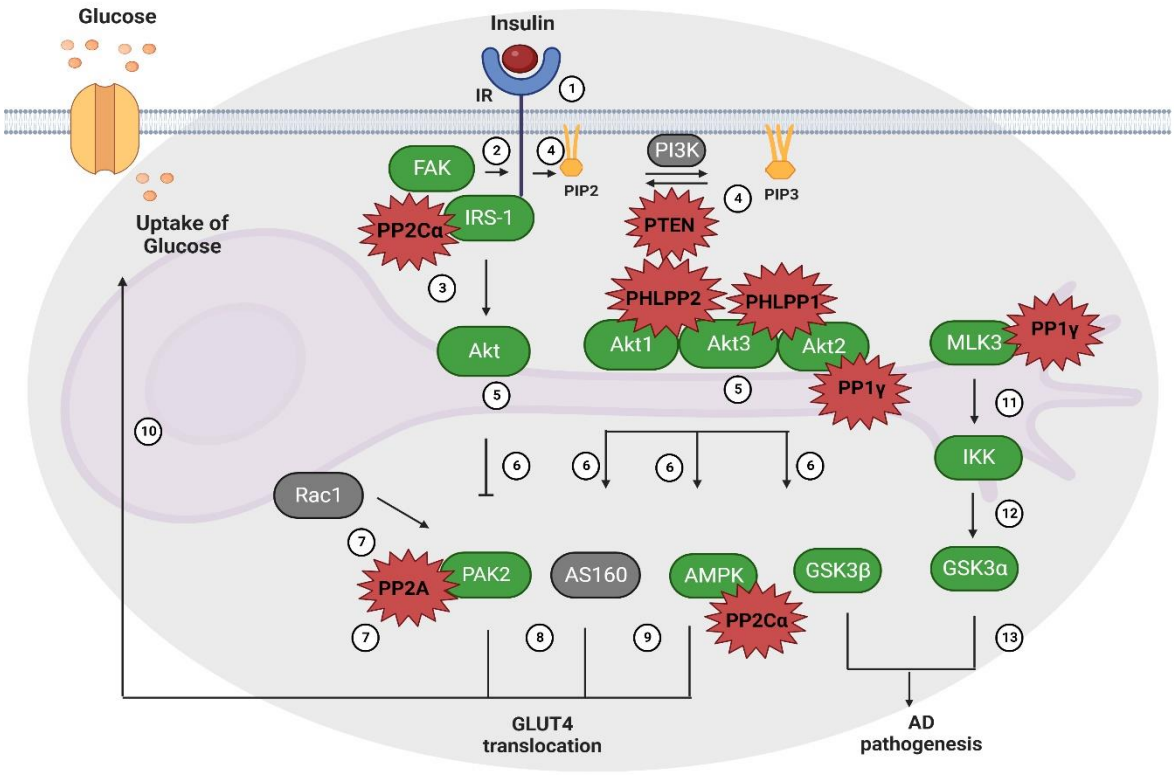
PP1 belongs to PPP family of Ser/Thr phosphatases composed of heterodimers of catalytic and regulatory subunits (Peti *et al.* 2013). The binding combination of catalytic and regulatory subunits provide the substrate specificity to the enzyme. Human genome encodes three isoforms of PP1 catalytic subunits namely PP1α, PP1β and PP1γ and over >200 regulatory subunits (Peti *et al.* 2013). PP1γ catalyzes large number of dephosphorylations and regulates variety of cellular processes like cellular metabolism (Comerford *et al.* 2006), cell survival (Trinkle-Mulcahy *et al.* 2006) and cell proliferation (Bao *et al.* 2016). Despite PP1γ being reported to be highly expressed in brain (da Cruz e Silva *et al.* 1995), the role of PP1γ in regulating neuronal insulin signaling is yet to be established. Recently, we have seen the role of PP1γ in regulating neuronal insulin signaling and insulin resistance (Yadav….& **Dey.** 2023). Isoform specific downregulation studies of PP1α and PP1γ demonstrated that PP1γ and not PP1α, regulates the neuronal glucose uptake. It does so by specifically dephosphorylating Akt2 (one of the isoforms of Akt). This was the first study which demonstrated the isoform specific role of PP1 where one isoform of a phosphatase i.e., PP1γ regulated neuronal insulin signaling by acting on another isoform of a kinase i.e., Akt. (Yadav ….& **Dey.** 2023). Not only neuronal glucose uptake, PP1γ was also found to regulate the Alzheimer's disease (AD) pathogenesis by regulating the activities of GSK3 isoforms differentially. As neuronal insulin resistance is already reported to be associated with increasing the onset of Alzheimer's Disease and within the repertoire of various kinases, GSK3 is one of the important kinases reported heavily to be associated with AD (Toral-Rios *et al.* 2020). Interestingly, we observed that PP1γ regulates both the isoforms of GSK3 i.e., GSK3α and GSK3β through two different kinases (Yadav ….& **Dey.** 2023).The regulation of GSK3β by PP1γ was happening directly through Akt2 while MLK3 dephosphorylation by PP1γ regulated the activity of GSK3α. Because of two different regulations of two isoforms of GSK3, controlled by PP1γ, the hallmarks of AD pathogenesis were also regulated differently. We observed that on one hand PP1γ was increasing the formation of Aβ plaques, one of the AD hallmarks while on the other hand decreasing another (formation of Neurofibrillary Tangles) AD hallmark (Yadav…& **Dey.** 2023. Such novel regulation by PP1γ can prove PP1γ as a possible and new linker connecting insulin resistance and AD.

PTEN:

Several laboratories identified a putative tumor-suppressor gene at 10q23 that encodes a 403 amino acid protein with a protein-phosphatase domain, which was then named PTEN for phosphatase and tensin homolog deleted on chromosome 10 (Myers *et al.* 1997). The PTEN protein contains five major domains: the N-terminal PIP2-binding domain (PBD), the catalytic domain of the phosphatase, the C2 domain, the C-tail domain, and the PDZ-binding domain (PDZ/BD); the C-terminal PDZ/BD domain (Masson & Williams 2020). PTEN-lipid-phosphatase activity dephosphorylates PIP3 to form PIP2, and it then antagonizes PI3K and blocks the activation of Akt, PTEN-protein-phosphatase activity dephosphorylates many

downstream targets (Liu *et al.* 2022). Thus, PTEN phosphatase activity can dephosphorylate multiple substrates, playing diverse roles in cellular function, including inhibiting cell adhesion and migration and maintaining genomic integrity (Milella *et al.* 2015). Apart from the tumor suppressor role, PTEN has also been studied in insulin signaling. PTEN, acts as a negative regulator of PI3K-Akt pathway, dephosphorylates PIP3 to PIP2 to leading to perturbations in insulin signaling cascade (Wijesekara *et al.* 2005). Several mutations in PTEN have been linked to cause defects in insulin signaling. Grinder-Hansen et al (2016) reported loss of function mutation in PTEN positively regulated insulin signaling. While whole-body PTEN KO mice have been reported to be embryonic lethal (Kimura *et al.* 2003), metabolic tissue-specific PTEN KO has been implicated in defective glucose homeostasis and insulin resistance (Wijesekara *et al.* 2005; Tong *et al.* 2009). Several studies have reported important role of PTEN in the brain metabolism as well. Plum et al (2006) reported that PTEN KO in POMC neurons lead to elevated hyperpolarization of POMC neurons, affecting food intake. This was attributed to increased ATP-sensitive potassium channel activity (K-ATP). This study established role of PTEN in K-ATP channel hyperpolarization by modulating PIP3. Subsequent studies also correlated this PTEN dependent K-ATP channel hyperpolarization in hypothalamus, ultimately regulating hepatic glucose production (HGP)by suppressing the hepatic vagus nerve efferent (Pocai *et al.* 2005). Kimura et al (2016) also reported that suppressed vagal output downregulated α-7 nicotinic receptors, affecting IL-6 signaling in hepatic Kupffer cells. This IL-6 signaling in hepatic cells promotes STAT3 activation, which affect G6Pase and PEPCK, decreasing HGP (Inoue *et al.* 2006). Importantly, we and others have reported PTEN play a role in regulating neuronal insulin signaling and resistance by dephosphorylating and inhibiting FAK at Tyr397 (Tamura *et al.* 1998; Gupta & **Dey** 2012). We show PTEN knockdown lead to increased FAK activity, regulating extracellular signal-regulated kinase 1/2 (ERK1/2) and affecting insulin signaling (Gupta & **Dey** 2012). Previously, some studies have reported different signaling in metabolic tissues versus neurons. FAK and ERK has been prime examples of such differences. While ERK promotes cell growth, neuronal ERK promotes neuronal death (Subramaniam *et al.* 2004). Similarly, FAK in metabolic tissue is a positive regulator of neuronal insulin signaling (Bisht *et al.* 2007; Gupta & **Dey** 2012). Thus, neuronal PTEN KD studies establish important role of PTEN in regulating neuronal insulin signaling and resistance by regulating FAK-ERK1/2 pathways. Further studies are very much necessary to firmly put PTEN in the realm of regulation of insulin signaling and insulin resistance in neuronal system.

From a variety of kinases and phosphatases known to be involved in insulin signaling, considerable information about neuronal insulin signaling has been discussed in this review. While there are several classes of proteins contributing to the signaling cascade, we have focused on key kinases and phosphatases, regulation and balance of which is necessary for proper insulin signaling. It is very interesting to note that, despite being insulin responsive, neurons behave different than other insulin responsive tissue like skeletal muscle, adipocytes and hepatocytes. For example, few kinases like FAK were reported as a negative regulator of insulin signaling (Huang *et al.* 2002) while in neurons it regulates insulin signaling positively (**Fig. 1 step 2**) (Bisht & **Dey** 2008). This tissue specific regulation is due to the regulation through a phosphatase named PTEN (**Fig. 1 step 4**) (Gupta & **Dey** 2009). Similarly, PAK2 was not reported to be involved in insulin signaling but it negatively regulates neuronal insulin signaling (**Fig. 1 step 7**) (Varshney & **Dey** 2016). The regulation of PAK2 was independent of Akt but dependent on Rac1 and PP2A (**Fig. 1 step 6 and 7**) (Varshney & **Dey** 2016). Akt is another such kinase, which brings increased complexity to the cascade because of its isoforms. In other peripheral tissues, Akt2 is the predominant contributing isoform (Cozzone *et al.* 2008)



while all Akt isoforms differentially regulate neuronal glucose uptake under insulin sensitive and insulin resistant condition (**Fig. 1 step 5**) (Sharma & **Dey** 2021b). This tissue specific regulation is due to expression and subcellular localization of AKT isoforms (Sharma & **Dey** 2021b). Despite being an equally important players in neuronal insulin signaling and insulin resistance, phosphatases are much lesser studied than kinases. Emerging studies have now focused on role of few phosphatases in neuronal insulin signaling and insulin resistance (Gupta & **Dey,** 2009; Yadav & **Dey**, 2022a). Regulation of neuronal insulin signaling and insulin resistance by phosphatases emerged to be as interesting as kinases. For example, PHLPP isoform differentially regulates isoforms of Akt, with PHLPP1 regulating Akt2 and Akt3, and PHLPP2 regulating Akt1 and Akt3 (**Fig. 1 step 5**) (Sharma and **Dey**, 2022). This Akt isoform specific effects were extended to AS160 and neuronal glucose uptake, in insulin sensitive and resistant conditions. Another example of PPP family of Ser/Thr phosphatase regulating neuronal insulin signaling is PP1γ (Yadav…& **Dey.** 2023). It participates in neuronal glucose uptake by specifically acting on Akt2 (**Fig. 1 step 5**). Interesting fact about these two phosphatases is they both are negative regulators of neuronal insulin signaling and insulin resistance. In contrast, the other two phosphatases namely, PTEN (a lipid and protein phosphatase) and PP2Cα (a PPM family of Ser/Thr phosphatase) emerged out to be as positive regulators of neuronal insulin signaling (Gupta & **Dey**, 2012; Yadav & **Dey**, 2022a). In peripheral insulin tissues, PTEN negatively regulates glucose uptake via PI3k-Akt pathway

Fig 1: Schematic representation of regulation of neuronal insulin signaling by different kinases and phosphatases: When insulin binds to insulin receptor (IR) (step 1) it activates IR by a kinase FAK (step 2). Activated receptor mediates the binding of IR to IRS-1 (step 3), whose regulation is controlled through PP2Cα (step 3). Simultaneously, activated IR activates PI3K, which converts PIP2 to PIP3 at plasma membrane (step 4). PTEN, a lipid and protein phosphatase, converts PIP3 to PIP2 (step 4). Formation of PIP3 on plasma membrane recruits Akt and its isoforms (Akt1, Akt2 and Akt3) (step 5), initiating downstream signaling (step 6, 7, 8 and 9), ultimately regulating neuronal glucose uptake (step 10). Ser/Thr phosphatases also play a role in this regulation. PHLPP1 regulates Akt2 and Akt3 (step 5) while PHLPP2 regulates Akt1 and Akt3 (step 5). PP1γ specifically regulates Akt2 (step 5). Downstream of Akt and its isoforms are various other kinases like PAK2 (step 6), AMPK

(step 9) and GSK3β (step 6). PAK2 is regulated by Akt (step 6), Rac1 (step 7) and PP2A (step 7). AMPK is regulated by PP2Cα (step 9). Regulation of kinases like PAK2, AMPK and a RabGTPase AS160 contributes to GLUT4 translocation leading to glucose uptake (step 10). On the other hand, PP2Cα acts on MLK3 (step 11) and ultimately regulates the activity of GSK3α (step 12) via IKK (Step 11). Both GSK3β and GSK3α regulation contributes to AD pathogenesis (step 13). Green: Kinases; Red: Phosphatases; Others: Grey. (Created with BioRender.com)

(Wijesekara *et al.* 2005). However, PTEN positively regulates neuronal glucose uptake by FAK-ERK pathway (**Fig. 1 step 4)** (Gupta & **Dey** 2012). On the other hand, PP2Cα in adipocytes is known to positively regulate glucose uptake through PI3K (Yoshizaki *et al.* 2004), and it positively regulates neuronal insulin signaling and insulin resistance through different kinases, namely IRS-1 and AMPK (**Fig. 1 step 3 and 9**) (Yadav & **Dey,** 2022a).

While substantial information about neuronal insulin signaling has been now emerging, the information so far depicted the picture that neuronal insulin signaling is an entangled web woven through the threads of kinases and phosphatases. Thus, our contribution is to understand the intricate signaling network of kinases and phosphatases is required to achieve essential metabolic balance. Understanding the role of each component of neuronal insulin signaling will lead towards better understanding of the cascade. This might solve the progression of neuronal insulin resistance which could reduce the risk of various neurodegenerative disorders. It can be expected, in future that some of these components of neuronal insulin signaling can be effective to consider as possible drug targets. The complex regulation of neuronal insulin signaling through kinases and phosphatases can shift the equilibrium and it could be possible that targeting either of them will not only have the ability to overcome insulin resistance but will be beneficial for the neurodegenerative disorders in future.

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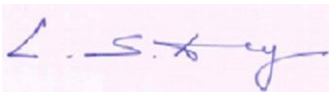

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