Chapter

Possibilities of Combinatorial Therapy: Insulin Dysregulation and the Growth Hormone Perspective on Neurodegeneration

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Abstract

RTKs have been reported to be implicated in several neurodegenerative disorders and the roles of insulin receptor family have emerged as a key common pathway across diseases. Thus we focussed on the Insulin receptor family and discussed the irregulation from the growth hormone axis. The signaling, regulation and physiology of the production in liver and CNS has never been discussed in signaling perspectives and is extremely crucial for understanding the possibilities of IGF1 in neurodegeneration specifically. The commonalities across neurodegenerative diseases such as oxidative stress, mitochondrial dysfunction, and protein misfolding and insulin pathway anomalies have been elucidated and correlated with the insulin pathway. The crosstalk possibilities of the pathways, along with other regulatory modes for the development of combinatorial therapy have been discussed to visualize a common platform for neurodegenerative diseases including AD, PD, HD, ALS and FTD. Furthermore, the incretin based therapies that have gradually emerged as alternatives for insulin based therapy due to its inherent drawback of resistance has been briefly discussed.

Keywords: neurodegeneration, insulin, IGF1, GPCR, combinatorial therapy, lncRNA, Alzheimer's disease

1. Introduction

Insulin dysregulation is a common phenomenon in several diseases, though their cause-effect relationship with progression is debatable. This review focuses on the degenerative pathways but essentially incorporates cues from proliferative mechanisms to develop a holistic approach towards understanding the disease progression. In case of neurodegeneration such as that in Alzheimer's disease [AD], Huntington disease [HD], Fronto temporal Dementia [FTD] and Parkinson's disease [PD], insulin dysregulation has been reported [1]. Therapies have been successfully developed encompassing the insulin pathway in ADwhere intranasal administration of insulin assists in recuperation, however resistance towards insulin and mode of administration remains an elusive matter [2]. Similar strategies are gradually being developed for FTD as well using Novolin-R insulin [3]. Insulin shock therapy for the schizophrenic patients was one of the initial

approaches towards tackling the disease, but with time insulin resistance or insensitivity to higher dosages led to search for better ways of ameliorating the disease on relapse [4]. Insulin like growth factor 1 [IGF1] therapy has been implemented in ADbut due to the lack of conclusive evidence, resistance and contentious results from experimental models, the attempt did not stand the test of time [5]. It is thus impending to further investigate the modes of regulation and pathways which could lead the therapeutic development.

Insulin receptor family is a subset of the broader Receptor Tyrosine kinase [RTK] family comprised of 20 precise receptor sub-families further sub divided into more families based on ligand and domains of the receptors that play varied roles in neurodegeneration [6]. They include ErbB, PDGF, Ins, VEGF, FGF, Trk, PTK7, Ror, MuSK, Met, Axl, Tie, Eph, Ret, Ryk, DDR, ROS, LMR, STYK1 and ALK [7]. Many of these families have been shown to be involved in AD, PD as well as proliferative diseases such as cancer. The alterations in expression as well as activity has been documented which clearly elucidates the importance of understanding the roles of these receptors in disease pathology. With respect to neurodegeneration however, the roles played by RTKs are gradually being explored and understood since the complexities both on the membrane front and intracellular pathways are numerous. Insulin receptor family composed of Insulin Receptor [INSR], Insulin like growth factor receptor [IGF1R, IGF2R], and Insulin receptor related receptor [INSRR] [8] forms a common bridge for understanding neurodegenerative pathways as they are implicated in almost all diseases and relatively well studied yet poorly understood. It is crucial to mention that unlike other members of the insulin family, INSRR is an orphan receptor with no known ligand. Recent studies have shown that it is pH sensitive and the receptor is activated by alkaline pH [9]. IGF2R unlike IGF1R is non-mitogenic and involved in targeting IGF2 to lysosomes for degradation. It basically functions in signal attenuation and on overexpression has been reported to increase the amyloid beta generation [10].

Thus we begin with an overview of the hallmarks of neurodegeneration, their underlying mechanisms in brief and then delve into the possibility of therapeutics encompassing insulin pathway as a future prospect for palliation of neurodegeneration. Insulin pathway involves mainly insulin andIGF1 which elicit different roles in the cell despite being structurally similar with common pathways that had been studied for decades but is still poorly understood in the context of neurodegeneration. Insulin pathway being a metabolic pathway primarily, is capable of modulating several downstream important signaling molecules and influences metabolism, growth and survival through P13K pathway and MAPK mediated pathway that determines cellular fate [11]. IGF1 additionally engages in the Jak–stat pathway [12] and uses several components of the GPCR pathways and in turn get regulated by them as well [13].

2. Commonalities of neurodegenerative diseases

Neurodegenerative diseases like Alzheimer's and Parkinson have been long studied and the key proteins identified have been tried and tested for targeting in order to ameliorate the disease. However most of it has failed [14]. Several mutations have been identified for both such as *APOEε4* allele, APP, PSEN1 and PSEN2 for AD, but people without any of these mutations have also been found to develop the disease [15], which adds to the complexity. The triggers for both these diseases have been shown to be associated with multiple factors as diverse as gut microbiota for PD [16], bacterial infections of the gum for AD [17], or genetic pre disposition and epigenetic modifications.

Patients with Huntington often develop diabetes, whereas those with diabetes are more prone to developing AD [18]. The impairment of insulin pathways is common across patients suffering from different neurodegenerative diseases. Studies with transfected striatal nerve cells in vitro, showed that IGF1 can block the mutant protein huntingtin-induced cellular death and decreases formation of intranuclear inclusions [19]. Reduction in apoptosis was perhaps not the reason for this observation since BDNF which does the same, did not prohibit formation of such inclusions. The mitochondrial dysfunction in these striatal cell lines derived from huntingtin Knock-in mice is perhaps ameliorated by insulin and IGF1. The roles of these factors have further been observed in several studies where reduced energy metabolism in lymphoblasts derived from HD patients was shown to be associated with downregulation of Akt and Erk activation which can be helped with IGF1 and insulin [20].

ALS and FTD are different diseases but both elicit a degeneration of neurons, their clinical as well as pathological manifestations are similar. Interestingly both of these display alterations in Growth hormone and IGF1 secretions [21]. ALS was initially characterized by the mutation in a gene, Superoxide dismutase [SOD1] with a 10–20% incidence in patients and since then more than a hundred different types of SOD1 mutations that cause ALS has been discovered [22]. The trigger for ALS and proposed mechanism though could be through growth hormones anomaly, could as well be through glutamate-induced neurotoxicity with an aberrant increase in glutamate concentration in CSF [23].

The aggregated proteins form intra cellular inclusions or extra cellular aggregates in different brain areas. These proteins usually have a beta -sheet structure that allows aggregation and fibril formation as part of the misfolding process [24]. Misfolding of protein aggregates is one of the key underlying cause of neurodegeneration. Amyloid fibrils form plaques found in AD, Phosphorylated tau leads to neurofibrillary tangles, prions mediate in neurodegeneration and alpha synuclein aggregates in PD are also common [25].

In case of PD, ALS and AD, upto10% cases are inherited. However, in HD almost every case has a familial history [26]. The common disease/common variant [CD/CV] hypothesis explains that common disorders are governed by common DNA variants which elevates risks but are usually not causative factors and might add to the understanding of genetic involvement in phenotypic manifestation of disease [27]. For example, the Apolipoprotein E [APOE] encodes a 299 amino acid long glycoprotein and is estimated to be a major contributing factor in AD development. It has also been reported in PD [27]. This similarity further elicits that neurodegenerative disorders might have a common underlying protein–protein interaction network (**Figure 1**). Also, intervention for neurodegenerative disorders could be facilitated by exploring the genes and its regulatory components including ncRNAs that might govern the progression and allow scope of regulating the protein–protein network downstream [28, 29]. Studies have focused on individual disorders but rarely generated a common platform that allows better understanding of the network by taking varied disorders into perspective.

Amongst the hallmarks of neurodegeneration that significantly contributes towards the progression is oxidative stress. It has been implicated in several diseases, including AD, PD and ALS [30]. Extensive oxidation of lipids, DNA and proteins leads to deactivation of major processes or upregulation of toxic cellular cascades. The imbalance in the scales of Reactive oxygen species [ROS] generation damages the cells [31]. Amyloid beta which is originally generated by neurons in AD in response to insults and cellular damage in pursuit of protection, in turn coordinates iron and copper to generate peroxide that accelerates ROS generation by Fenton chemistry [14]. Dopamine buildup in cytoplasm in PD coordinates iron and induces ROS formation. Active site destabilization of SOD also allows further oxidation. Such unregulated

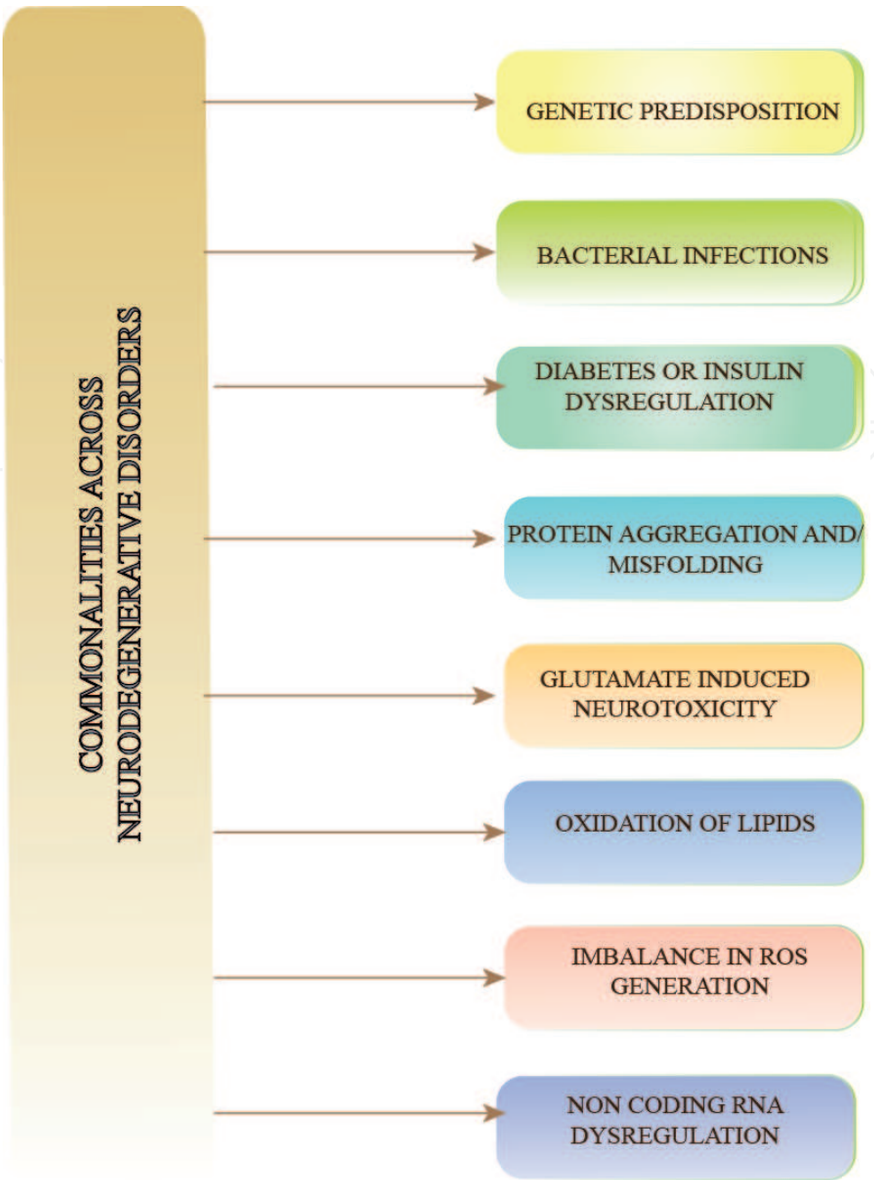

Figure 1.
Commonalities across neurodegenerative disorders, two or more are often shared.

ROS further affects calcium regulation which leads to excitotoxicity [32]. The current drugs encompassing ROS generation affect the rate of progression at late stages and thus it is increasingly important to understand the growth hormone axis that changes early in the disease cycle and determines the final outcome, ROS generation and toxic misfolding of proteins aggregates amongst other catastrophic events that lay ahead of the domino like cascade of neurodegenerative pathways.

3. Insulin resistance and neuroinflammation

The growth factors bind to receptors and they no longer respond to the ligand binding when resistance develops, which would have otherwise triggered a cascade of downstream signaling. Several studies have attempted to evaluate the total IGF1 or Insulin levels that are responsible for the resistance to overcome it. Dosage up to 100 nM Insulin even instead of physiologically relevant 1 nM have been unsuccessful in reinstating the sensitivity. This further drives attention towards the receptor [33]. The anomalies in the reports pertaining to the receptor stimulation

particularly in AD clearly elucidate a faulty signaling cascade operating at different stages of the disease [2]. The receptors of the Insulin family, vis-à-vis INSR and IGF1R are elusive and bind to both ligands, Insulin and IGFs. Their diverse intracellular domains allows them to bind several other adaptor proteins other than the conventional mediators of signaling cascade, IRS1 and IRS2 [34]. There are numerous astounding facts about these receptors which make them unique targets and add to their therapeutic value. INSR and IGF1R forms hybrids that has a higher affinity for IGF1 [35–37] but their activity if its varied from individual dimers and their respective localization after stimulation is unknown. The insulin resistance poses a major setback to its therapeutic value and correcting the axis by identifying other players in the cascade both downstream and at the membrane front could thus help in re-sensitizing the receptors.

Both Insulin and IGF1R has been shown to enter the nucleus when activated recently and it is speculated that they perform physiological roles which might be altered in different disease situations [38]. It has been experimentally illustrated as an orchestrated event that occurs physiologically in non-cancerous cell lines along with different cancers, in which this behavior of nuclear migration was first found. It however remains due to illustrate the proportions of the nuclear and cytoplasmic amount of IGF1R in different disease conditions where these metabolic signaling pathways are known to be altered. Their phosphorylation status too remains to be explored since IGF1R has multiple phosphorylation sites [39] and they could be important in understanding their role in neurodegeneration.

Recent studies show that phosphoINSR can be translocated into the nucleus in a clathrin mediated manner. It forms a complex with RNA pol-II, HCF 1 and DNA binding transcription factors like THAP 11. Mass-spectrometry data shows the translocation involves KPNA 2 and HSP 70 [40].

IGF-1R has been observed in the nucleus in case of prostate cancer and breast cancer cells. Full length IGF-1R alpha and beta chains were reported in the nuclear extract of prostate cancer cells. This is the only example of a receptor which traffics as individual sub unit to the nucleus [41]. Other RTKs such EGFR, FGFR has also been previously been observed in the nucleus. The endocytosis is here both clathrin and caveolin mediated. The nuclear transport here is not mediated by adaptor proteins like IRS 1 or an inherent NLS but by SUMOylation [42].

The cause and effect relationship for the ever so complex pathway and its involvement in AD or PD remains unclear and further experimental studies are required to investigate the connection of this underlying nuclear migration with disease progression. The ligands and receptors need to betreated an individual elements instead of a holistic component in the cascade, since there remains the possibility that Insulin and IGF1 both can stimulate other receptors [43]. The concerned receptors could be activated in diseases like AD by Amyloid beta fragments [44, 45] and behave differently in terms of interacting partners and localization, thus altering the signaling cascade majorly.

4. Insulin as a growth factor with prospects in therapeutics for neurodegeneration

Insulin production in the body was assumed to primarily happen in the pancreas and circulated throughout, however production in the CNS of both insulin and IGF1 is now proven [46–48]. Insulin production in CNS appears to be important for the lower organisms than that in higher organism like humans. However further research in the last decade has yielded results that clearly indicate that insulin is secreted in the CNS and might play important roles in physiology. The amount of the same is

presumed to be lower compared to the pancreas derived insulin which is transported into the brain through receptor mediated transcytosis. However it can also be independent of the receptor as illustrated by [49]. Insulin circulating in the bloodstream binds to receptors present on the endothelial cells at the blood brain barrier which is further moved into the interstitial fluid. There it binds to insulin receptors distributed throughout the cerebral cortex, olfactory bulb, hippocampus, hypothalamus, amygdala and septum [48]. IGF1 on the other hand, binds to one of its 6 binding proteins and remains in the inactive form in the bloodstream and in local tissues. The entrance into the brain occurs in a similar fashion as in the case of insulin [50].

Several parts of the brain are sensitive towards insulin and they have a different relationship associated with the alterations of the levels. Neuroimaging studies have shed light on the insulin induced brain responses in the fusiform gyrus, hippocampus, pre-frontal cortex, striatum, hypothalamus and insular cortex. Thus healthy insulin signaling controls brain networks implicated in reward processing, memory retrieval, homeostatic control and cognitive control in general [51]. These wide involvements of insulin in regulation of distinct parts of the brain responsible for different activities leads to the marked impact of a mild dysregulation and thus indicate an alteration could infact be an initial event in the cascade of neurodegeneration.

Insulin is known to activate cell growth, cell repair, mitochondrial activity, gene expression, energy utilization and protein synthesis for decades. In both AD and PD, insulin signaling pathway and downstream regulators contribute significantly to the pathology of the disease. Insulin signaling in the brain of these patients is desensitized and while analyzing post-mortem brains, it appears that they have inactivated receptors and downstream IRS1 and 2 as well. The key secondary messengers of this signaling pathway, Akt and mTOR also appears to be inactivated in these patients as it is observed diabetes [14, 20, 27]. Thus, AD was termed as Type 3 diabetes where a systemic resistance to the pathway occurs [52]. However, unlike diabetes the reasons could be very different. Insulin desensitization occurring in the brain could be part and parcel of the inflammatory response in the brain. In case of AD, where amyloid beta aggregates lead to plaque formation, the oxidative stress and cytokines involvement in the long run could restrict the supply of the insulin and IGF essential for growth and repair of the neurons [53]. Pro-inflammatory cytokines like Tumor necrosis factor [TNF] could possibly block the signaling pathways of insulin and IGF1.

Saenger et al. [54] investigated into the SOD1-G93A mouse lines that elicit ALS like pathology, both mild and severe phenotype form. The results indicated IGF1 therapy in the early stages can be effective but in case of severe cases, the functional outcomes were no better. Despite increase signaling in brain, at high doses, survival chances did not improve. Clinical trials that evaluated the role of Growth hormones in patients with ALS yielded mixed results. Researchers back in 1993 employed a very small dosage [0.1 mg/day] which impacted the IGF1 levels after therapy. In another study recently in 2012, 2.8 mg/day was used, but that further led to a reduction in the IGF1 and IGF1-BP3 demonstrating the effectiveness of the therapy further [46].

5. IGF1 as a pleiotropic factor in aging and neurodegeneration

The brain receives its IGF1 supply through both autocrine and paracrine pathways. IGF1 is secreted by liver, in response to binding of growth hormone [GH] to their respective GH receptors, which leads to increase in the circulating IGF1 levels. The IGF1 thus secreted by liver then binds to their receptors IGF1R in the pituitary and hypothalamus, which in turn inhibits Growth hormone releasing hormone [GHRH] and Growth hormone [GH] production [46].

The hepatic IGF1 production makes up for 70% of the total circulating ligand pool and caters to the brain by passing through the blood brain barrier at choroid plexus directly into the Cerebrospinal fluid [CSF] with the assistance of IGF1R and Megalin, a low density lipoprotein receptor related protein 2 transporter [46]. There is a clear feedback loop for the hepatic production regulation, but not for the autocrine production in the brain (**Figure 2**). Studies show mutations that manifest in GH deficiency or resistance present normal cognitive functionality [55] however when IGF1 production is globally eradicated or insensitivity is induced, that leads to microcephaly and cognitive deficits in children [56]. This suggests the autocrine brain production might be preserved in GH mutated scenarios and a separate feedback loop exists for that regulation. Adding to the complexity, the circulated IGF1 is bound to IGF binding proteins [IGFBPs] mainly IGFBP-3 being the most abundant, making them unavailable for receptor stimulation [57].

The autocrine production though expected to be independent of the hepatic IGF1 production, appears to decline with age similarly. The endocrine decline in IGF1 levels has been related to the diminished GH pulse frequency and amplitude, observed in case of aging. It is partly due to the decrease in ghrelin binding to GH secretagogue receptor [GHSR] [57]. Aging and lowering of cognitive abilities is observed to be associated with lower levels of IGF1, where the receptor levels increase to compensate

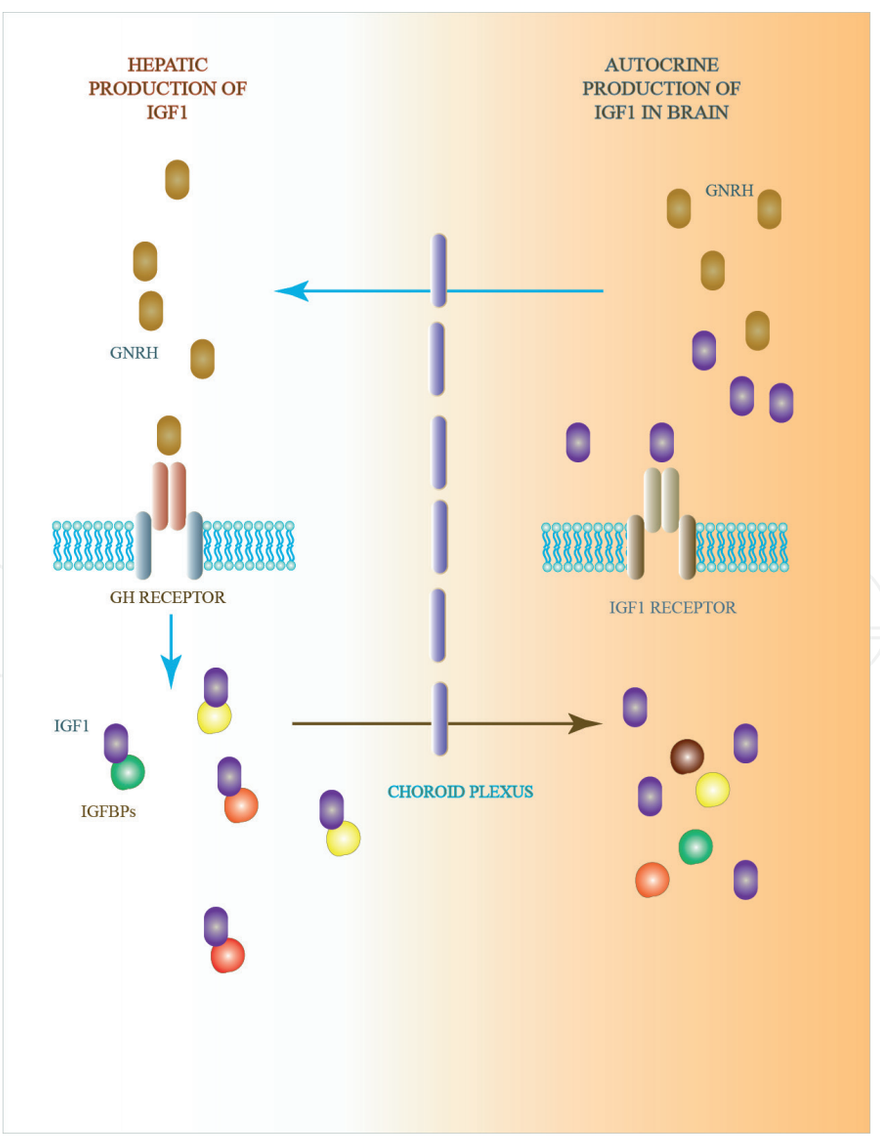

Figure 2.
Feedback loop for hepatic and autocrine production of IGF1 in the brain.

for the lower availability perhaps. The increase in the receptor levels in aged individuals could also be a coping mechanism for combating insults and stress induced due to the breach in blood brain barrier. Nevertheless, it is evident that IGF1 plays a major neutrophic role within PNS and CNS and is strongly involved in neurogenesis, anti-apoptotic, synaptogenesis and anti-inflammatory effects at cortical, sensory and motor levels and hence further investigation into the puzzling characteristics of the receptor shall shed light on the definitive involvement in neurodegeneration.

IGF1 other than being implicated in AD and other neurodegenerative diseases is also a major risk factor for cancer. Its upregulation is a major implication of proliferation in several cancers. Modulation of the cell cycle, apoptosis and cell survival through interaction with IRS1 and IRS2 and downstream effectors like PI3K/AKT/mTOR allows IGF1 to drive the cell towards proliferation [58]. Some pre-clinical studies state that mutations in genes that control the GF/INS/IGF axis can increase the lifespan even in invertebrate and vertebrate animal models [59].

Aging and IGF1 are intertwined on several levels, adding to the complexity of the insulin pathway. Research shows IGF1 deficiency could slower aging [60–63] and thus is a separate concern for therapy development for patients who develop Late onset AD [LOAD]. However combinatorial treatment with other membrane receptor antagonists or agonists for that matter which are implicated in the diseases could offer better options for prophylaxis.

6. Impact of growth factors on the neurophysiology

The amyloid hypothesis that focuses primarily on the protein misfolding that occurs in AD and aggregation associated with it largely fails at analyzing the actual neuronal pathophysiological developments in the brain. Inflammatory mediators like cytokines can promote the state in CNS through several mechanisms, crossing the BBB or entering by circumventricular organs, communication transmitted via the vagal nerve, and signaling through the cerebral endothelium [51]. These pathways allow insinuation and perpetuation of pro-inflammatory responses within the brain. Amyloid beta oligomerisation and tau phosphorylation which are hallmarks of AD can also be promoted through such changes [51].

The impact of growth factors comes into play since important cellular phenomena like inflammation and underlying reasons for neuronal loss are in turn corrected with insulin based therapies. The problems with such therapies persist, and have been long known, as progressive resistance. Key growth factors present in the brain such as BDNF, NGF, GDNF, IGF1 and insulin all lose their capacity of reversing or controlling the damage over time [64]. However, the improvements are often long lasting and disease progression is halted effectively by them through receptors in the glia initially [51]. Neurodegenerationis a complex process andfactors like GLP1, GIP1, and insulin cross the blood brain barrier in order to provide protection on several levels including ROS generation. In response to these, synaptic activity as well as plasticity is restored, brain functionality and memory retention is improved, and mitogenesis and mitochondrial function which dysregulates the energy utilization is also corrected [65]. Autophagy occurs normally and apoptosis rates are reduced as well.

7. Future prospects: cross talk between insulin signaling and other pathways

In order to improve the capabilities of the insulin therapy and circumvent the issues with hyperinsulinemia, it is important to understand the crosstalk

possibilities for this important axis. The goal to re-sensitize the cells towards treatment or induce a similar cascade by receptor stimulation through other ligands or adaptors could pave the way for combinatorial therapy. Thus, understanding the cross talk possibilities for neurodegenerationis impending. In case of heart diseases a crosstalk between insulin receptors and beta 2 adrenergic receptors [β_2AR] is found which paved the path towards understanding the exploitation of GPCR signaling pathways by RTKs [66]. RTKs can use Beta arrestin, G protein receptor kinases, insulin to directly induce tissue RAS activation, regulate beta-adrenergic catecholamine stimulation and even to attenuate contractile response to β_2AR stimulation in myocardial ischemia [67].

Angiotensin II [AII] acts on the cell by virtue of its receptor and since 1996, the direct connection between the two pathways on the phosphorylation and the downstream P13K activity has been known. Stimulation with AII inhibited both basal and insulin stimulated PI3K activity in rats [68].

Amongst interesting findings, IGF1R has been found to exist in association with $GABA_B$, which offers neuroprotection to cerebellar granule neurons from low potassium induced apoptosis. This process involves Akt recruitment and activation of IGF1R with the assistance of $G_{i/o}$- protein and FAK1 [69, 70]. Antidepressants can potentially trans-activate RTKs like EGFR by inducing activation of LPA receptors [71]. Reports show that acute MOR agonists can induce beta arrestin dependent and src-dependent IGF1R transactivation through subsequent Erk phosphorylation, prolonged treatment with the agonist however leads to heterologous desensitization of IGF1R based cascade [72]. The studies corroboratively indicate insulin GPCR heterocomplex plays important roles in different tissues and several of such associations could be involved in neurons in physiological and disease scenarios as well.

Studies show IGF1 receptor signaling and anti-apoptotic activity in cortical neurons is partly due to the Src dependent PACAP type I receptor which is transactivated [73]. Non-canonical insulin pathway receptors like TrkA has also been observed in such complexes with another receptor LPA1 that allows for constitutive activation of the cascade involving ERK1/2 in response to NGF [71]. IGF1 can also mediate G protein dependent ERK1/2 activation through transactivation of sphingosine 1 phosphate receptors [73].

Dopamine and Insulin signaling pathways are also intertwined as they elicit a reciprocal relationship. Antagonism of D2 receptors for a short duration leads to upregulation of insulin secretion [74]. Insulin can also enhance reuptake of dopamine, which has been visualized with respect to mental health and metabolic syndromes.

Recent studies on ncRNAs are also evolving and shows that several lnc RNAs and miRs that are involved in controlling key phenomena in neurodegenerative diseases like AD, PD, HD and ALS. Long non-coding RNAs like BACE1-AS, XIST are upregulated in AD [75, 76]. Neat1 and MALAT1 are upregulated in FTD as well as ALS, where they form paraspeckles with TDP-43 and FUS proteins. UCHL1-AS1 leads to perturbation of ubiquitin-proteasome system that and is upregulated in PD. HTT-AS, HAR1 and BDNF-AS were reported to be dysregulated in HD. Interestingly, insulin responsiveness of these genes have not been explored in neuronal perspective. Some lncRNAs such as H19, lncASIR have been reported by several groups [29, 77] but their implications and involvement, interaction with other proteins or ncRNAs shall open up avenues for therapy oriented research. Furthermore, Lnc RNAs that are known to interact with these receptors such as IRAIN, GAS5, NNT-AS1 [78] needs to be studied in the neurodegenerative landscape to allow translational medicine development.

8. Combinatorial and peptide based therapies: insulins, incretins and drugs

Insulin resistance remains a major challenge towards drug development and meanwhile alternative strategies encompassing hormones are being tested and developed forneurodegenerative diseases. Incretin hormones like GLP1 and GIP show similar therapeutic roles and do not lead to insulin desensitization, as they do not activate the receptors however they lend similar effects [79]. Furthermore, analogues of the peptide hormones do not affect the blood glucose levels in non-diabetics with normoglycemic index. The side effects are mild loss of appetite and nausea. Detemir study led to this important realization that drugs for non-diabetic with AD or PD who require intervention with hormones needs to be developed with caution. Those with higher peripheral insulin resistance performed better with the drug, however those with lower peripheral resistance suffered from worsening of memory formation. Though there is plenty to understand and explore about the insulin pathway and its role in complex multifactorial neurodegenerative diseases, the treatments encompassing these factors that appears to be effective must be discussed.

GLP1 is part of a peptide based growth factor family that activates a glucagon type GPCR, expressed in primates, rodents and human neurons. Other receptor agonists such as lixisenatidemliraglutide and semaglutide available for treating Type II diabetes are also being tested for eeffectiveness in AD and PD [1]. Some of them can traverse the blood brain barriers and are thus prospective game changers for therapeutics. GLP 1 mimetic have shown promising results in animal models of AD, they exhibit fascinating reduction of chronic inflammation which is a major driver for progression of disease.

GIP is another sister incretin that bind to a GPCR on the membrane and its receptor is abundant in a wide range of cells including pyramidal neurons, Purkinje cells in cerebellum and basal brain areas. It was capable of offering neuroprotection to APP/PS1 mice, reduced loss of synapses and recreated synaptic plasticity [79]. Furthermore, the amyloid plaque load was also reduced along with oxidative stress and DNA damage.

9. Conclusions

Substantial advancement in the field of growth hormone, RTKs and their involvement in neurodegeneration has been made in the last two decades. The development of peptide based therapies involving incretins that can mitigate the degenerative processes in the brain is a major feat that shows promise. Controlling this major InsR and IGF1R, which are prominent and one of the most important albeit in age reversal [61, 80] is yet to be achieved but picking up cues from diseases like cancer that elicits an alternate pathway [81], in terms of therapy could accelerate the process of developing therapies (**Figure 3**). The ability of growth factors to modulate cellular events such as ROS generation, energy utilization and others are remarkable and thus developing more sophisticated approaches using the knowledge thus gathered to invoke the right set of signals for slowing the cycle and early detection are important. Though possibilities involving the insulin pathway have been only explored on the protein level, regulation on the RNA level could be utilized yet to enhance sensitivity.

Pre-clinical studies from growth hormone therapies often leave out important aspects like multiple binding partners, transactivation and cross talks that leads to different results when applied to humans. Research on analogues with no resistance, compounds that re-instate sensitivity and alternative drugs such as mAbs against

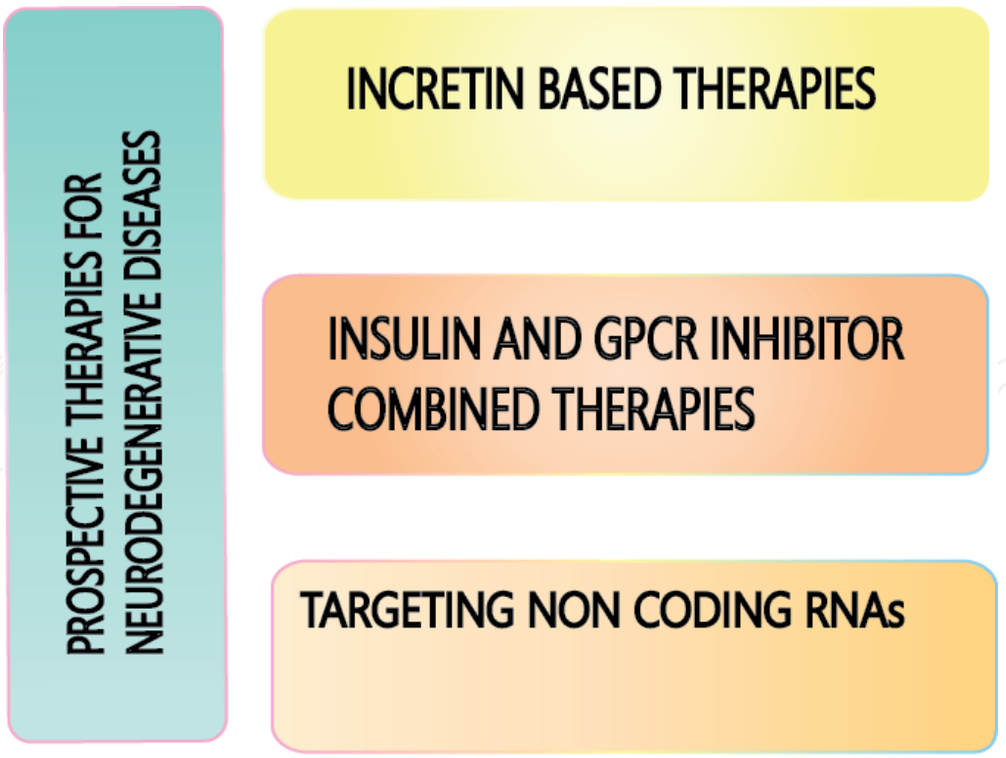

Figure 3.
Therapies that could exploit the unified approach and yield therapeutic benefits.

RTKs altered are the need for the hour. The current peptide based drugs on the market are promising since they can potentially reverse a range of pathophysiological parameters of neurodegeneration. However understanding the hormonal axis that led to the death is important for further biomarker development and therapy development as well. The growth hormone axis could indeed be an underlying cause amongst the plethora of factors already known for neurodegeneration. Studies on their involvement in determining cellular fate and their tuning in accordance with progression of disease are required for developing a better understanding about stages of the progressive disorders discussed holistically. The crosstalk with other pathways and gradual involvement of several miR and Lnc RNA which are crucial are complicating the story and yet simplifying it in terms of the puzzling and contentious results.

In conclusion, it is apparent that the neurodegenerative disorders have an underlying insulin pathway abnormality and growth hormone axis plays a major role the CNS and in turn affects progression of neurodegeneration. The Insulin receptor family amongst the RTKs is an important set that could lead the path towards therapies for degenerative disorders in a non-invasive manner if understood in their entirety and the regulation though complex could be a common network of protein–protein interaction that would simplify prognosis and prophylaxis.

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Conflict of interest

The authors declare no conflict of interest.

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