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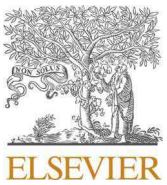

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Protective role of IGF-1 and GLP-1 signaling activation in neurological dysfunctions

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ABSTRACT

Insulin-like growth factor-1 (IGF-1), a pleiotropic polypeptide, plays an essential role in CNS development and maturation. Glucagon-like peptide-1 (GLP-1) is an endogenous incretin hormone that regulates blood glucose levels and fatty acid oxidation in the brain. GLP-1 also exhibits similar functions and growth factor-like properties to IGF-1, which is likely how it exerts its neuroprotective effects. Recent preclinical and clinical evidence indicate that IGF-1 and GLP-1, apart from regulating growth and development, prevent neuronal death mediated by amyloidogenesis, cerebral glucose deprivation, neuroinflammation and apoptosis through modulation of PI3/Akt kinase, mammalian target of rapamycin (mTOR) and mitogen-activated protein kinase (MAPK/ERK). IGF-1 resistance and GLP-1 deficiency impair protective cellular signaling mechanisms, contributing to the progression of neurodegenerative diseases. Over the past decades, IGF-1 and GLP-1 have emerged as an essential component of the neuronal system and as potential therapeutic targets for several neurodegenerative and neuropsychiatric dysfunctions. There is substantial evidence that IGF-1 and GLP-1 analogues penetrate the blood-brain barrier (BBB) and exhibit neuroprotective functions, including synaptic formation, neuronal plasticity, protein synthesis, and autophagy. Conclusively, this review represents the therapeutic potential of IGF-1 and GLP-1 signaling target activators in ameliorating neurological disorders.

Abbreviations: AAV, Adeno-associated viruses; Aβ, Amyloid-β; AchE, Acetylcholinesterase; AD, Alzheimer's disease; Akt, Ak strain transforming; AMP, Adenosine MonoPhosphate; Ang1, Angiopoietin-1; ASD, Autism spectrum disorder; ATP, Adenosine Triphosphate; BBB, Blood Brain Barrier; BDNF, Brain-derived neurotrophic factor; BMI, Body mass index; BTBR, Black and Tan BRachyury; cAMP, Cyclic Adenosine MonoPhosphate; cDNA, Complementary DNA; CHD8, Chromodomain-helicase-DNA-binding protein 8; CNS, Central nervous system; CSF, Cerebrospinal Fluid; CVAs, cerebral vascular accidents; DAT, Dopamine transporter; DSM, Diagnostic and Statistical Manual of Mental Disorders; eNOS, Endothelial nitric oxide synthase; EPAC, Exchange Proteins directly Activated by cAMP; ERK, Extracellular signal-regulated protein kinase; FC, Functional connectivity; FGF, Fibroblast growth factor; GABA, Gamma-Aminobutyric acid; GDP, Guanosine Diphosphate; GFAP, Glial fibrillary acidic protein; GHRH, Growth-hormone-releasing hormone; GIP, Gastric inhibitory polypeptide; GLP-1, Glucagon like peptide-1; GLP- 1, Glucagon like peptide-1 receptor; GPCR, G-protein coupled receptor; Grb-2, Growth factor receptor-bound protein 2; GSK3-β, Glycogen synthase kinase 3-beta; GTP, Guanosine triphosphate; HbA1c, Hemoglobin A1c; HD, Huntington's disease; HI, Hypoxic ischemia; HPA, Hypothalamic–pituitary–adrenal; HTT, Huntingtin; i.g., intragastrically; i.n., Intranasal; i.p., Intraperitoneal; IGF-1, Insulin like growth factor-1; IGF-1R, Insulin like growth factor-1 receptor; IL-6, Interleukin; iNOS, Inducible nitric oxide synthase; IRS, Insulin receptor sustrate; LTP, Long term potentiation; MAPK, mitogen-activated protein kinase; MEK, Mitogen-activated protein kinase kinase; MI, Myo-inositol; mRNA, messenger RNA; mTOR, mammalian Target of Rapamycin; NAAG, N-acetylglutamate; NAC, N-acetyl cysteine; Nf-1, Neurofibromatosis 1; PD, Parkinson's disease; PI3k, 3-Phosphoinositide-dependent kinase 1; PIP3, Phosphatidylinositol (3,4,5)-trisphosphate; PKA, protein kinase A; PKB, protein kinase B; Ps9, Pseudogene 9; Raf, Rapidly Accelerated Fibrosarcoma; Ras, Rat sarcoma; REM, Rapid eye movement; ROS, reactive oxygen species; RTT, Rett syndrome; s.c., Subcutaneous; SCI, spinal cord compression injury; Ser, Serine; SH2, Src homology 2; Shc, Src homology 2 domain containing transforming protein; SOS, Son of Sevenless; TBI, Traumatic brain injury; TGF-β, Transforming growth factor; Thr, Threonine; VEGF, Vascular endothelial growth factor; VGCCs, Voltage gated calcium channels.

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1. Introduction

IGF-1, often known as Somatomedin C, is a multifunctional polypeptide mitogen associated with the insulin gene family (Zheng et al., 2000). IGF-1 is a basic peptide possessing a molecular weight of 7649 daltons (Laron, 2001). It includes 70 amino acid residues linked together by three disulfide bonds (Rinderknecht and Humbel, 1978). It is produced on a cellular level in various tissues, including the brain, where it performs paracrine functions (Russo et al., 2005). Further, it is secreted into the bloodstream and directed toward distant tissues as part of the somatotrophic axis (hormonal function) (Delafontaine et al., 2004). IGF-1 exerts its actions via interaction with cell surface receptors (Czech, 1989; Dai et al., 1992). The type I IGF receptor is a heterotetramer composed of paired, disulfide-linked α-and β-subunits, considered the major transducer of IGF signals (Adams et al., 2000). Its expression in all neural cells is inevitable throughout the lifetime (Sun, 2006). The α-subunits are extracellular and bind IGFs, whereas the β-subunits are present throughout the cell membrane and possess a tyrosine kinase downstream mechanism (Jacobs et al., 1983; Rubin et al., 1983). The type 1 IGF receptor is transcribed by a single gene exhibiting a structural resemblance to the insulin receptor (Foti et al., 2004).

The major CNS cell types in the hypothalamus, hippocampus, cerebellum and cortex produce IGF-1 (Mairet-Coello et al., 2009; Madathil et al., 2013; Sanz-Gallego et al., 2014; Chaker et al., 2016).

IGF-1 deficiency leads to increased oxidative damage to the brain, causes edema, and impairment in learning and memory processes, which can get restored with IGF-1 replacement therapy (Puche et al., 2016). A systematic anatomical evaluation of the brains of IGF-1 -/- mice revealed decreased brain size, hypomyelination of the central nervous system, and loss of neurons from the hippocampus and striatum (Beck et al., 1995). Previously, it has been investigated that IGF-1 concentrations less than 9.4 nmol/l are correlated with a reduction in the speed of processing information and a decline in cognition (Dik et al., 2003). Also, IGF-1 deprivation induces cerebromicrovascular malfunction and neurovascular dissociation, reflecting the ageing phenotype and thus is a major contributor to cognitive impairment (Toth et al., 2015). Furthermore, astrocytic infiltration is another abnormal function associated with IGF-1 scarcity in the brain (Yan et al., 2014). Organ hypoplasia occurs in mice with null mutations in the genes expressing insulin-like growth factor 1 (IGF 1) and IGF-1 receptor (IGF-1R) (Liu et al., 1993). Additionally, reduced cognitive function, neuronal ageing, and neurodegeneration are linked to an age-related reduction in the levels of circulating IGF-1. Recently, it has been reported that aberrant central IGF-1 signalling promotes age-related cognitive deficits and abnormalities by reducing mitochondrial activity (Pharaoh et al., 2020).

Glucagon-like peptide 1 (GLP-1) is classified as a peptide hormone with a sequence of 30 amino acids (Simsir et al., 2018). It is produced and secreted by intestinal epithelial endocrine L-cells, pancreatic alpha cells, and neuronal units in the CNS (De Graaf et al., 2016). It is synthesized via differential processing of proglucagon and preproglucagon, two genes expressed predominantly in the distal ileum and colon L cells, as well as neurons (Holst, 2007; Baggio and Drucker, 2007). The GLP-1 receptor, recognized as class B GPCR, is the critical mediator of normal human physiology and serves as a valuable drug target for many diseases, including diabetes, metabolic syndrome, osteoporosis, and CNS disorders (Wu et al., 2020). The GLP-1R regulates the mechanistic physiological response to the GLP-1, a prominent target involved in type 2 diabetes and various neurodegenerative disorders (Koole et al., 2013).

GLP-1 receptors are present throughout the brain, majorly in the arcuate nucleus, paraventricular nucleus, and dorsomedial nucleus of the hypothalamus, along with central amygdale (Cork et al., 2015). They are also found on the cell membrane of pyramidal neurons in the hippocampus and neocortex, facilitating learning (Hamilton and Hölscher, 2009). Overall, GLP-1 receptors are widespread and located in the globus pallidum, caudate-putamen, thalamus and cerebral cortex (Alvarez et al., 2005). It has been previously reported that GLP-1 receptors exhibit a significant role in neuroprotection (During et al., 2003). GLP-1 insufficiency impairs memory formation and disrupts long-term synaptic potentiation (Abbas et al., 2009). The leptin receptors deficiency in neuronal cells expressing GLP-1 located in the solitary tract nucleus resulted in hyperphagia and obesity (Scott et al., 2011). It is currently investigated that deletion of the specific postnatal GLP-1 receptor (GLP-1R) in astrocytes expressing glial fibrillary acidic protein compromises mitochondrial integrity. Additionally, it initiates a combined stress response by increasing the synthesis of fibroblast growth factors and cerebral glucose utilization (Timper et al., 2020).

It can allude from the above data that IGF-1 and GLP-1 signaling mechanisms in the brain can be beneficial for treating various neurological diseases. The protective actions exerted by these two cellular targets in the brain are significant and will serve as the basis for future neurological research. It has been investigated that GLP-1 analogues exert their actions by activating IGF-1R in stroke conditions (Huang et al., 2020). Therefore, there is a link between the two signaling pathways, but further research would strengthen the fact that IGF-1 and GLP-1 modulate each other's signaling. The different IGF-1 and GLP-1 analogues have been investigated preclinically and clinically as the therapy for neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, Huntington's disease, Ischemic stroke, Autism etc. This review aims to discuss the IGF-1 and GLP-1 analogues employed as recent therapeutic interventions to prevent and treat several neurocomplications. The neuroprotective action of IGF-1 and GLP-1 receptor activators in various neurodegenerative and neuropsychiatric disorders has been discussed based on clinical and preclinical evidence.

2. Normal regulation of IGF-1 and GLP-1 in the brain

IGF-1 exerts its neuroendocrine pleiotropic effect by interfering with various central nervous system processes such as growth, proliferation, neurogenesis, and cell migration (Kappeler et al., 2008; Nieto-Estévez et al., 2016). IGF1R has increased expression levels in circumventricular organs and the pituitary and cerebellum, indicating a prominent role in neurodevelopment and sensory integration (Kleinridders, 2016). Recently, it has been investigated that IGF-1 centrally can restore cognitive and sensorimotor functions (Farias Quipildor et al., 2019). Furthermore, it has been proved that IGF-1 stimulates neuronal differentiation and controls dynamic changes in neuronal polarity during the migration of neurons in the cerebral cortex (Nieto Guil et al., 2017). Neurogenesis is another crucial function of IGF-1 that helps brain growth and development (Yuan et al., 2015; Laron, 2001).

GLP-1 also exerts its anti-inflammatory response by expressing GLP-1R in astrocytes and glial cells during neuroinflammation (Iwai et al., 2006). GLP-1 hinders glucose uptake and enhances fatty acid oxidation, mitochondrial integrity, and its function in cultured astrocytes (Timper et al., 2020). Furthermore, GLP-1 has been investigated to demonstrate its major role in learning, neuronal proliferation, and neurogenesis (McGovern et al., 2012). Recent research reported that enhanced cognitive function and reduced brain glucose uptake were associated with an increase in central GLP-1 (Ruze et al., 2021).

2.1. Physiological role of IGF-1 in the brain

When the ligand (IGF-1) binds to the IGF1R, the receptor domain of tyrosine kinase is autophosphorylated and initiated, resulting in the binding and phosphorylation of insulin receptor substrate (IRS) proteins (Girnita et al., 2014). IRS proteins, including IRS1, IRS2, and IRS4 (IRS4 expressed mainly in the hypothalamus), are critical components of the IGF-1 signaling pathway (White, 2014). They provide a hub for dual signaling pathways: phosphoinositide 3-kinase (PI3K)-AKT, also referred to as protein kinase B (PKB), and mitogen-activated protein kinase-extracellular signal-regulated kinase (MAPK-ERK) (Duda et al., 2018). When PI3K interacts with IRS proteins, the catalytic subunit of PI3K is activated, and phosphatidylinositol 4,5-bisphosphate to

phosphatidylinositol (3,4,5)-triphosphate (PIP3) takes place. Subsequently, phosphoinositide-dependent protein kinase 1 binds PIP3. It phosphorylates AKT, enabling downstream signaling pathways such as the mammalian target of rapamycin complex 1 and forkhead box O (FoxO) signaling, consequently regulating the protein content of neurons, synaptic plasticity, autophagy and neuronal proliferation (Gabbouj et al., 2019). IGF-1 activation of the MAPK-ERK pathway, the other prominent cascade downstream of IRS proteins, affects neural growth, proliferation and differentiation (Vogel, 2013). The adaptor molecules in the SH2 domain, known as growth factor receptor-bound protein 2 (Grb2) and Shc interact with activated receptors and IRS proteins in this region. Further, Grb2 interacts with son-of-sevenless (SOS) that activates the guanine nucleotide-binding protein Ras by catalyzing the release of GDP (inactive Ras) and the binding of GTP (active Ras) (Hall et al., 2020). As a consequence, Ras activation initiates the downstream kinase cascade, consisting of Ser/Thr kinase Raf, that further stimulates mitogen-activated protein kinase (MEK), followed by phosphorylation of ERK1 and 2, hence controlling neuronal proliferation and promoting cell survival (Krishna and Narang, 2008). The significance of IGF1 signaling in regulating the normal physiology of the brain was first recognized in the 1980 s, with IGF1 signaling primarily described as a significant growth factor for the brain, regulating neurogenesis, neuronal survival, and myelination (Kappeler et al., 2008).

2.2. Physiological role of GLP-1 in the brain

GLP-1 readily enters the blood-brain barrier and binds to its receptors throughout the brain (Kastin et al., 2002). GLP-1r via Gαs

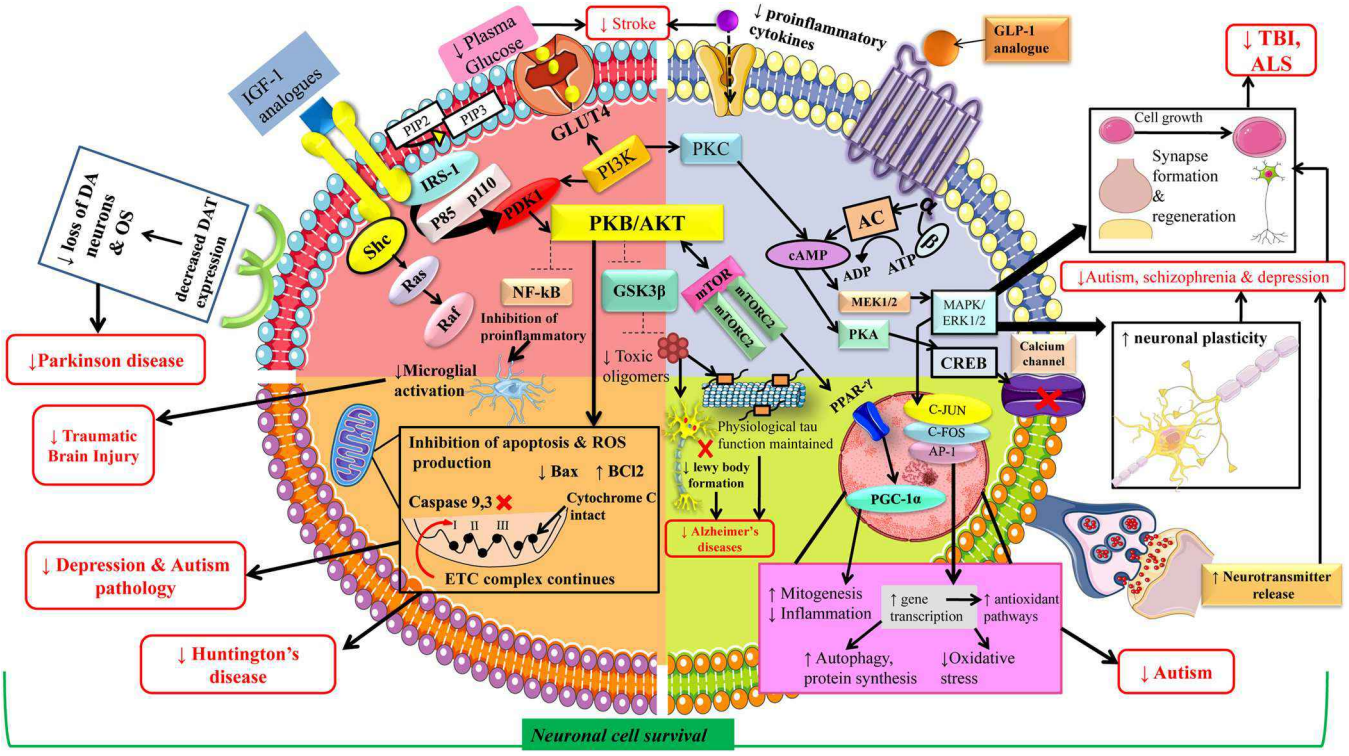

Fig. 1. Pharmacological actions of IGF-1 and GLP-1 receptor activators with different diseases. The schematic illustration depicts the possible role of IGF-1 and GLP-1 receptor agonists in alleviating various neuropathological conditions. IGF-1R analogues bind to their receptor, restoring the PI3k/Akt/mTOR signaling pathway, inhibiting neuronal apoptosis and ROS production, and thus ameliorating the pathological conditions of depression, autism, and Huntington's disease. GLP-1R activators restore PI3k functioning, which results in the translocation of GLUT-4 to the plasma membrane, thereby increasing glycolysis during ischemic stroke. Inhibition of NF-kB by IGF-1 analogues results in decreased microglial activation, which contributes to improving TBI and stroke conditions. Additionally, Akt inhibits GSK-3β, which reduces toxic oligomers, resulting in the maintenance of physiological tau function and suppression of lewy body formation, thus ameliorating the neuropathological conditions associated with Alzheimer's disease. Akt phosphorylates FoxO-1, inhibiting its transcriptional functions, which are required to activate antioxidant pathways. Additionally, activation of PPAR- gamma by Akt promotes mitogenesis and decreases inflammation, leading to cell survival. The downregulation of mTOR promotes autophagy and protein synthesis. The activation of the GLP-1 receptor by its various analogues activates the MAPK/ERK1/2 pathway, resulting in increased gene transcription and a reduction in oxidative stress. Additionally, activating MAPK/ERK1/2 improves TBI, autistic, schizophrenic, and depressive-like conditions by promoting cell growth, synaptic formation, and regeneration. The stimulation of the GLP-1 receptor increases cAMP production, which enhances neurotransmitter release, thereby eradicating neuro complications associated with autism, schizophrenia, and depression. Increased cAMP levels activate PKA, which activates calcium channels. Reduced expression of dopamine transporters decreases dopamine neuron loss and oxidative stress, thereby ameliorating Parkinson's disease motor deficits. Conclusively, activators of the IGF-1 and GLP-1 receptor promote neuronal cell survival and alleviate the various neuropathological factors associated with multiple neurological diseases. Abbreviations: IGF-1 = insulin like growth factor-1; GLP-1 = Glucagon like peptide-1; shc=Src homology 2 domain containing transforming protein; Grb- 2 = Growth factor receptor-bound protein 2; Sos=Son of Sevenless; Ras=Rat sarcoma; Raf=Rapidly Accelerated Fibrosarcoma; IRS-1 = insulin receptor substrate-1; BCl-2 = B-cell lymphoma 2; Bax=Bcl-2 Associated X-protein; Caspase=cysteine-dependent aspartate-directed proteases; PIP2 =Phosphatidylinositol 4,5-bisphosphate; PIP3 = phosphatidylinositol (3,4,5)-trisphosphate; PDK1 = 3-Phosphoinositide-dependent kinase 1; PI3k = 3- Phosphoinositide-dependent kinase 1; PLC=phospholipase C; PKA=protein kinase A; PKB=protein kinase B; Akt=Ak strain transforming; mTOR=mammalian target of rapamycin; EPAC=Exchange Proteins directly Activated by cAMP; ETC=electron chain transport; SOD1 = superoxide dismutase; ROS=reactive oxygen species; MAPK=mitogen-activated protein kinase; MEK=Mitogen-activated protein kinase; ERK1/2 = extracellular signal-regulated protein kinase; CREB=cAMP-response element binding protein; GDP=Guanosine Diphosphate; AC=adenylyl cyclase; cAMP=Cyclic Adenosine Mono-Phosphate; GLUT4 = glucose transporter 4; GSK3-β = Glycogen synthase kinase 3-beta; NF-kB=nuclear factor kappa-light-chain-enhancer of activated B cells; NT=neurotransmitter; LTP=long term potentiation; AP-1 = Activator protein 1; nNOS=neuronal nitric oxide synthase; DAT=dopamine transporters; AD=Alzheimer's disease; TBI=Traumatic brain injury; OS=oxidative stress activation inhibition.

stimulates adenylate cyclase and increases cyclic AMP (cAMP) levels (Drucker et al., 1987). The enhanced cAMP induces intracellular signaling that is mediated by protein kinase A (PKA) and exchange proteins that are activated by cAMP (EPAC) dependent activities. The activation of the pathways mentioned above enables GLP-1 to trigger a wide range of actions within the cell, eventually resulting in insulin release and genetic changes (Baggio and Drucker, 2007; Cho et al., 2014; Holst, 2007; MacDonald et al., 2002; Seino and Shibasaki, 2005). GLP-1 is reported to inhibit ATP-regulated potassium channels via cAMP-dependent downstream mechanisms, including PKA and EPAC (Kang et al., 2006; Nakazaki et al., 2002; Shiota et al., 2002), enhance the activity of particular L-type voltage-gated calcium channels (VGCCs) (Britsch et al., 1995), and opens up the non-specific cation channels (Kang et al., 2006; Holz et al., 1995). When these mechanisms are combined, they increase calcium influx, thus enhancing insulin secretion. Additionally, it promotes physiological benefits in the brain, such as increased neuronal progenitor proliferation, enhanced long-term potentiation (LTP) in the hippocampus, improved learning, decreased plaque development and inflammation in the brain, and enhanced neuroneogenesis (Femminella et al., 2019). The restoration of the normal functioning of the IGF-1 and GLP-1 signaling cascade with their activators has been illustrated in Fig. 1.

3. Abnormal functioning of IGF-1 and GLP-1 signaling in the brain

3.1. IGF-1 dysfunctioning in the brain

IGF-1 is a critical neurotrophic protein essential for optimal brain development, cell survival, and growth (Zheng and Quirion, 2004). Numerous studies have shown that IGF-1 deficiency, specifically in the brain, results in various abnormalities, including neurodegeneration. For instance, preclinical research revealed that mice without *Igf1* gene have a significant hearing impairment and several abnormalities in the inner ear involving spiral ganglion. Their findings indicated a decrease in the area and size of the deficient mice's cochlear nuclei and cell loss in the cochlear nuclei (Fuentes-Santamaría et al., 2016). According to a recent study, alterations in IGF-1 levels in neural tissue following HI may

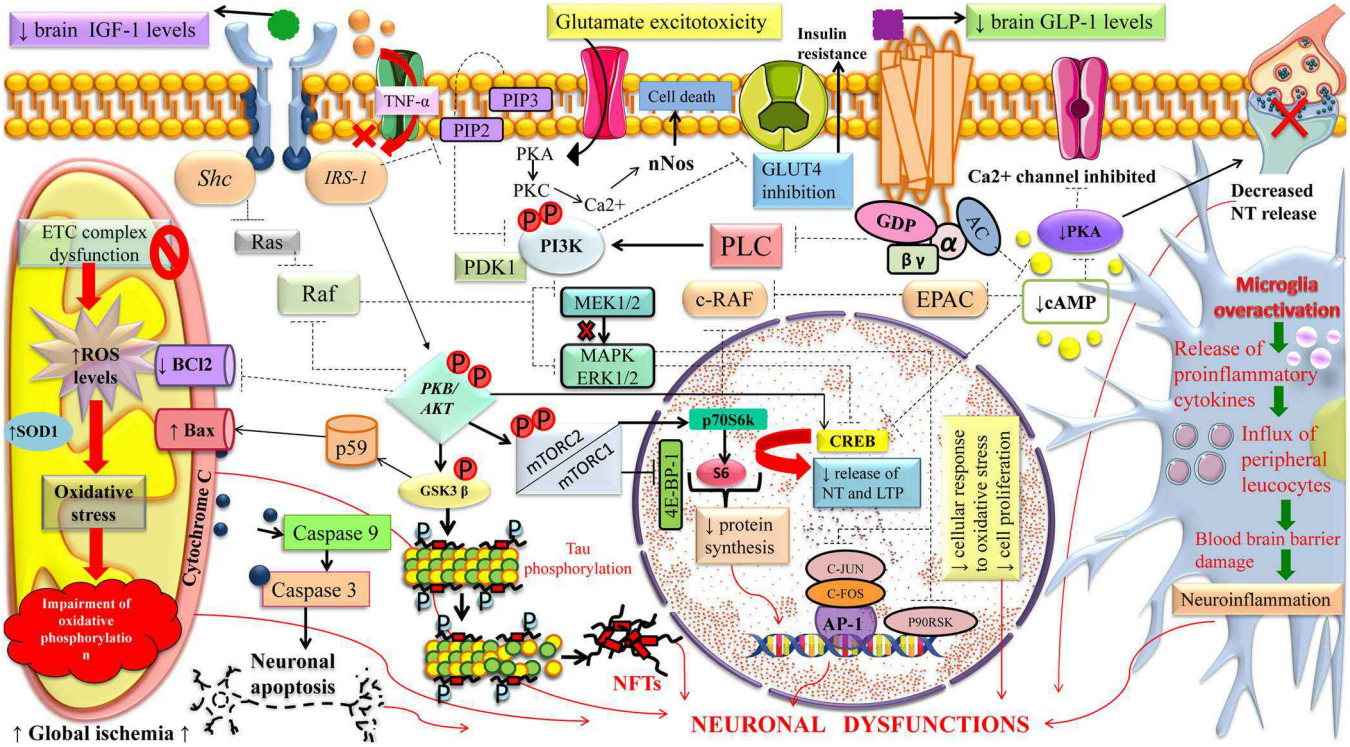

Fig. 2. Involvement of IGF-1 and GLP-1 in etiopathogenesis of neuronal dysfunctions. Reduced IGF-1 and GLP-1 levels in the brain have been demonstrated to cause IGF-1 and GLP-1 receptor downregulation. The dysregulation of the several secondary messenger pathways, including PI3K/Akt/mTOR and MAPK/ERK1/2, results in neuronal apoptosis, reduced protein synthesis, decreased neurotransmitter release, and a decline in the long term potentiation. GSK3-β activation causes tau phosphorylation leading to the formation of neurofibrillary tangles. Moreover, overactivated mTOR causes the overexpression of the P70S6K that leads to reduced protein synthesis. Downregulation of MAPK/ERK signaling cascade causes inhibition of P90RSK gene resulting in decreased cellular responses to oxidative stress and halting cell proliferation. Additionally, reduced glutamate uptake from synaptic clefts causes glutamate excitotoxicity, which stimulates PKA/PKC. Then, the IRS-1 complex is directly inhibited by PKC, enhancing the intracellular Ca2 + that produces nNos causing cell death. Furthermore, the release of TNF-α inhibits the IRS-1 complex aggravating neuro complications. On the other hand, GLP-1 receptor downregulation causes a decrease in cAMP and PKA levels that inactivates calcium channels and a reduction in neurotransmitter release. Suppression of GLUT-4 impairs the translocation process, resulting in insulin resistance and glycolysis disruption. Mitochondrial dysfunction occurs due to disruption in the electron transport chain that increases SOD1 and ROS levels producing oxidative stress. Lastly, microglial overactivation followed by proinflammatory cytokines secretion results in neuroinflammation. In a nutshell, dysregulation of the IGF-1/GLP-1 receptor results in chronic progression of various neurological dysfunctions. **Abbreviations:** IGF-1 =insulin like growth factor-1; GLP-1 =Glucagon like peptide-1; shc=Src homology 2 domain containing transforming protein; Ras=Rat sarcoma; Raf=Rapidly Accelerated Fibrosarcoma; IRS-1 =insulin receptor substrate-1; BCl-2 =B-cell lymphoma 2; Bax=Bcl-2 Associated X-protein; Caspase=cysteine- dependent aspartate-directed proteases; PIP2 =Phosphatidylinositol 4,5-bisphosphate; PIP3 =-phosphatidylinositol (3,4,5)-trisphosphate; PDK1 = 3-Phosphoinositide-dependent kinase 1; PI3k= 3-Phosphoinositide-dependent kinase 1; PLC=phospholipase C; PKA=protein kinase A; PKB=protein kinase B; Akt=Ak strain transforming; mTOR=mammalian target of rapamycin; EPAC=Exchange Proteins directly Activated by cAMP; ETC=electron chain transport; SOD1 =superoxide dismutase; ROS=reactive oxygen species; GSK3-β = Glycogen synthase kinase 3-beta; MAPK=mitogen-activated protein kinase; MEK=Mitogen-activated protein kinase kinase; ERK1/2 =extracellular signal-regulated protein kinase; CREB=cAMP-response element binding protein; GDP=Guanosine Diphosphate; AC=adenylyl cyclase; cAMP=Cyclic Adenosine MonoPhosphate; GLUT4 =glucose transporter 4; NT=neuro-transmitter; LTP=long term potentiation; AP-1 =Activator protein 1; nNOS=neuronal nitric oxide synthase inhibition; activation.

contribute to the subsequent white matter abnormalities, such as delayed oligodendrocyte growth, reported in newborns exposed to perinatal hypoxia (Janowska et al., 2020). Another research concluded that blocking IGF-1 exacerbated inflammatory responses in SCI lesions and neuropathic pain in SCI rats (Yao et al., 2021). Moreover, a study reported that reduced circulating IGF-1 relates to cognitive dysfunction and memory impairment in sevoflurane-induced aged mice (Jiang et al., 2017). Lastly, it is reasonable to conclude that a deficiency of IGF-1 in neuronal cells results in abnormal physiology, which inevitably causes neurodegeneration.

3.2. GLP-1 dysfunctioning in the brain

GLP-1 dysfunction results in decreased insulin secretion by reducing the proliferation of β-cells, increasing apoptosis and causing a glucose homeostasis imbalance (Huang et al., 2015). GLP-1 downregulation causes oligodendrocyte deterioration, demyelination, glial hyperactivity, immunological dysregulation, and neuroexcitation in the brain (Shandilya et al., 2021). According to a recent study, there is downregulation of GLP-1 and GLP-1R in the brains of AD patients and mice models, and the abnormalities may be associated with memory deficits and neurodegeneration (Chen et al., 2019). By enhancing apoptosis, inflammation, and glial activation, GLP-1 receptor disruption results in retinal neurodegeneration (Hernández et al., 2016). These findings prove that GLP-1 or GLP-1R disruption impairs neuronal cell function. The dysfunction of IGF-1 and GLP-1 is depicted in Fig. 2.

4. Involvement of IGF-1 and GLP-1 activators in various neurological disorders

The IGF-1 and GLP-1 receptor activators are the recent emerging therapeutic agents being investigated for their efficacy in neurodegenerative, neuropsychiatric and neurological dysfunctions. The various preclinical investigations (Table 1) and clinical studies (Table 2), employing IGF-1 and GLP-1 receptor analogues demonstrate their critical role in treating CNS complications. Several neurodegenerative diseases are enlisted below, involving IGF-1 and GLP-1 activators as potential treatment therapies.

4.1. Alzheimer's disease (AD)

AD is a neurodegenerative disease most frequently indicated by loss in memory and cognitive deterioration (Dubois et al., 2021). Memory loss is often referred to as a primary finding in the prior clinical stages of AD (Aisen et al., 2017). The deficiency in cholinergic neurons (H Ferreira-Vieira et al., 2016), toxic amyloid-beta (Aβ) accumulation (Selkoe and Hardy, 2016), hyperphosphorylation of tau protein (Lewis and Dickson, 2016), synaptic dysregulation (Briggs et al., 2016), oxidative stress (Kumar and Singh, 2015), and neuroinflammation (Calsolaro and Edison, 2016) have all been suggested to be responsible for development AD pathology. Neuropsychiatric symptoms associated with AD typically manifest themselves in three stages: irritability, depression, and changes in nighttime behavior; agitation, anxiety, apathy and appetite changes; and finally, hallucinations, elation, delusions, disinhibition and motor disturbances (Masters et al., 2015; Lanctôt et al., 2017). IGF-1 and GLP-1 have been studied and beneficial in various preclinical and clinical studies involving AD.

The researchers supposed that insulin-like growth factor-1 (IGF-1) could help central nervous neurons regulate glucose metabolism, which is used to treat various neurodegenerative diseases such as AD (Cheng et al., 2000). It has been clinically identified that IGF-1 inducer GHRH administration improved cognitive deficits by elevating the GABA and N-acetylaspartyl-glutamate (NAAG) in adults with AD (Friedman et al., 2013; Baker et al., 2012). In the human neuroblastoma cell line SHSY5Y, it has been discovered that IGF-1 protects against A25–35 toxicity via the PI3K/Akt/FOXO3a pathway, which involves the inhibition of PUMA expression and the activation of Bax (Hou et al., 2017). Additionally, crocin combined with endurance training, instead of administered alone, may significantly affect the enhanced IGF-1 content in the hippocampus of rats with AD (Negarandeh et al., 2019). Serrapeptase or nattokinase administration daily for 45 days in a rat model of AD resulted in a reduction in brain AchE activity, TGF-β, Fas, and IL-6 levels, as well as a rise in BDNF and IGF-1 levels when compared to control rats (Fadl et al., 2013).

Liraglutide has been clinically shown to increase glucose metabolic rate and cognitive abilities while decreasing Aβ deposition (Femminella et al., 2019; Gejl et al., 2016). Additionally, it has been claimed in an in vitro study that it inhibits apoptosis, autophagy, and cellular cytotoxicity (Liu et al., 2016). Genoposide has been studied to determine that it increases the expression of the inactive form of GSK3 (pS-9) and decreases tau phosphorylation, thereby preventing spatial learning deficits (Gao et al., 2014). GLP-1 analogues penetrate the blood-brain barrier and can lower Aβ levels that help prevent Aβ-induced neurotoxic effects such as inflammation and improve indicators of learning and memory (McClean et al., 2011). Liraglutide and lixisenatide have been investigated in recent in vivo studies to reduce tau phosphorylation, amyloid-βbeta plaque, and neurofibrillary tangles, thereby improving memory in AD (Qi et al., 2016; Chen et al., 2017; Cai et al., 2018). The dual and triple agonists of GLP-1 and GIP are a promising neuroprotective effects in AD (Cao et al., 2018; Tai et al., 2018). The above findings combined to demonstrate the potential benefits of IGF-1 and GLP-1 analogues on the key pathological aspects of AD. This evidence suggests that IGF-1 and GLP-1 activators could be possible drugs in AD therapy.

4.2. Parkinson's disease (PD)

PD is a fatal progressive neurodegenerative disorder affecting between 1 % and 3 % of the world's over-60 population (Scorza et al., 2017; Hirsch et al., 2016). The neuropathology of PD is characterized by an abnormal loss of dopaminergic neurons in the substantia nigra, α-synuclein aggregation, and tau phosphorylation (Dickson, 2018). PD is distinguished by motor symptoms such as bradykinesia, slumped body posture, limb rigidity/tremors, dystonia, and other gait abnormalities (Sveinbjornsdottir, 2016). REM sleep behaviour disorder, restless leg syndrome, frequent nocturia, dysphagia, insomnia, hypersalivation, swallowing difficulties, constipation, and impotence are additional non-motor symptoms of PD (Jellinger, 2015).

IGF-1 has been shown to impact PD patients and rodent models positively. A recent study found anthocyanins from blackcurrants to protect against PD (Fan et al., 2018). IGF-1, vitexin, and NAC increase cell viability while decreasing cell apoptosis in human neuroblastoma cell lines (Hu et al., 2018; Cheng et al., 2016). Additionally, in preclinical studies, vitexin and ginsenoside Rg1 have been shown to reduce neurocomplications in animal models of PD (Hu et al., 2018; Xu et al., 2009).

GLP-1 analogues have been studied successfully in PD patients and have demonstrated beneficial effects in animal models. Exenatide, a GLP-1 receptor agonist, has been investigated for its potential to improve cognitive deficits and clinical diagnostic scores in PD (Athauda et al., 2017; Aviles-Olmos et al., 2013). Preclinical research on GLP-1/GIP dual agonists indicates that they have the potential to significantly improve the neuropathological problems associated with PD (Ji et al., 2016; Yuan et al., 2017; Jalewa et al., 2017; Li et al., 2020). Furthermore, other GLP-1 analogues, such as exendin-1, liraglutide, lixisenatide, and semaglutide prevent motor impairments in animal models of PD (Liu et al., 2015; Zhang et al., 2018). In conclusion, these encouraging clinical and preclinical results indicate that IGF-1 and GLP-1 mimetics may have improving effects on neurocomplications associated with PD.

Table 1
Involvement of IGF-1 and GLP-1 receptor activators in various neurological diseases with preclinical evidences.

S. No.	Disease	Target involved	Target activator	Study type/species/ gender/age weight/ no. of species	Dose/Route	Study duration	Key findings	References
1	Alzheimer's Disease	↓ IGF-1	Crocin + endurance	In-vivo 30 Male Sprague-dawley rats, 8 weeks old, 250 ± 65.4 g	25 mg/kg, i.p. route	56 days	↑ IGF-1 levels ↑ glycogen in the hippocampus tissue	Negarandeh et al. (2019)
			Serrapeptase (SP) and Nattokinase (NK)	In-vivo 66 Male albino rats,120–150 g	(SP) dose: 10.8 U/kg bw, 21.6 U/kg bw, (NK) dose: 360 FU/kg bw, Oral route	45 days	↑ IGF-1 levels, BDNF levels, ↓ AchE activity, Fas, IL-6 levels, TGF-β	Fadl et al. (2013)
		↓ GLP-1	Geniposide	In-vivo 50 Adult male, Sprague Dawley rats, 220–250 g	50 μM in 3,5 and 10 μl CSF, ICV route	21 days	↑ GSK3β(pS-9) [inactive form] expression ↓ GSK3β(pY-216) [active form], tau phosphorylation prevents spatial learning deficit	Gao et al. (2014)
			Exendin-4	In-vivo 24 APPswePS1ΔE9 (C57BL/6) mice, 9 months old	25 nmol/kg, i.p. route	21 days	↓ levels of hippocampal IRS-1pSer JNK activation ↑ cognition	Bomfim et al. (2012)
			Liraglutide	In-vivo 48 APPswe/PS1DE9 (C57BL/6) male mice, 7 months old	25 nm/kg, i.p. route	56 days	↑ synaptic plasticity, dentate gyrus young neurons, ↓ glial activation, amyloid plaque load ↓ memory impairment, synapse loss	McClean et al. (2011)
				In-vivo 48 APPswe/PS1DE9 (C57BL/6) mice, 14 months old	25 nm/kg, i.p. route	60 days	↑ IDE levels, expression of insulin degrading enzyme, GSK3b (C) and Nrk2b ↓ glial activation, amyloid plaque load, memory impairment, synapse loss	McClean and Hölscher (2014a)
				In-vivo 60 Male C57/BL6 mice, 8 weeks old, 24–25 g	25 nmol/kg, s.c. route	56 days	↓ AβO levels, p-Tau levels, memory impairment	Qi et al. (2016)
				In-vivo 40 Wild-type C57BL/6 mice and 3 ×Tg mice, 7 months old, 25–32 g	300 μg/kg, s.c. route	56 days	↓ tau hyperphosphorylation, NFTs, neuronal degeneration ↑ memory	Chen et al. (2017)
				In-vivo 80 male Wistar rats, 10–12 weeks old, 307–412 g	0.2 mg/kg, s.c. route	28 days	↓ tau hyperphosphorylation	Yang et al. (2013)
			Lixisenatide Or Liraglutide	In-vivo 40–48 male APP/PS1 and wild-type C57/Bl6 mice, 7 months, 30 g	Lixisenatide: 1–10 nmol/kg, Liraglutide: 25 nm/kg 2.5 nmol/kg, i.p. route	70 days	↓ microglial activation, amyloid plaque load, LTP disruption	McClean and Hölscher (2014b)
			Lixisenatide	In-vivo Female APP/PS1/tau mice and C57BL/6 J Wild type mice,12 months old	10 nmol/kg, i.p. route	60 days	↓ amyloid plaque load, NFTs, neuroinflammation	Cai et al. (2018)
			DA5-CH (GLP-1/GIP dual agonist)	In-vivo 60 APPswe /PS1dE9 transgenic mice (30 male and 30female) and wild type C57BL/6 J, 9 months old	10 nmol/kg, i.p. route	28 days	↓ amyloid plaque load, tau hyperphosphorylation ↑ LTP, memory	Cao et al. (2018)
			GLP-1–GIP–glucagon agonist (triple agonist)	In-vivo 36 APP/PS1 transgenic mice, 6 months old	10 nmol/kg, i.p. route	60 days	↑ BDNF levels ↓ apoptosis, amyloid-β, neuroinfammation, oxidative stress, memory deficit	Tai et al. (2018)
2.		↓ IGF-1	Vitexin			15 days		

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Table 1 (*continued*)

S. No.	Disease	Target involved	Target activator	Study type/species/ gender/age weight/ no. of species	Dose/Route	Study duration	Key findings	References
	Parkinson's disease			In-vivo 32 Male C57BL/6 mice, 12 weeks old	50 mg/kg, Oral route		↓ initial lesions, cell apoptosis, caspase-3 activity, Bax/Bcl-2 ratio, bradykinesia	Hu et al. (2018)
			Ginsenoside Rg1	In-vivo 60 adult female Wistar rats, 220–250 g	10 mg/kg, i.p. route	15 days	↓ rotational behavior, neurotoxicity ↑ dopamine content, Bcl-2	Xu et al. (2009)
				In-vitro SK-N-SH cells	0.001– 1 μM	24 h	↑ Bcl-2 ↓ Bax, apoptosis	Gao et al. (2009)
		↓ GLP-1	Clostridium butyricum	In-vivo 30 Male C57BL/6 mice, 6–8 weeks, 18–22 g	5 × 108 CFU/ 0.2 ml/day/mice i.g. route	28 days	↓ dopaminergic neuronal loss, behavioral deficits, synaptic dysfunctions and gut microbiota dysbiosis ↑ level of colonic GPR41/43 and GLP-1, expression of cerebral GLP-1R	Sun et al. (2021)
			DA-JC1 (GLP-1 & GIP dual agonist)	In-vivo 50 Male C57BL/6 mice, 20–22 g	50 nmol/kg, i.p. route	7 days	↑ tyrosine hydroxylase (TH), BDNF levels	Ji et al. (2016)
			Exendin-4 + Liraglutide + Lixisenatide	In-vivo 96 C57Bl6 male mice, 8 weeks old, 25–30 g	Exendin-4 10 nmol/kg; Liraglutide 25 nmol/kg; Lixisenatide 10 nmol/kg, i.p. route	14 days	↓ apoptosis, dopamine synthesis, motor impairment	Liu et al. (2015)
			Semaglutide	In-vivo 72 male C57BL/6 mice, 10 weeks old, 20–25 g	25 nmol/kg, i.p. route	7 days	↓ motor impairments, Tyrosine hydroxylase levels, apoptosis,	Zhang et al. (2018)
			NLY01	In-vivo α-synuclein preformed fibril mouse model, 6 months old	3 mg/kg, s.c. route	150 days	↓ dopaminergic neuronal loss, behavioral deficits	Yun et al. (2018)
				In-vivo hA53T α-syn transgenic mice, 6 months old	3 mg/kg, s.c. route	120 days	↓ behavioral deficits	Yun et al. (2018)
				In-vitro Cultured microglial/ astrocytes	1 μM	1 day	↓ microglia-mediated conversion of astrocytes to a neurotoxic phenotype (A1) and microglial activation	Yun et al. (2018)
			GLP-1/GIP dual agonist DA3-CH	In-vivo 40 adult male C57BL/ 6 mice, 8 weeks old, 15–20 g	25 nmol/kg, i.p. route	7 days	↓ microgliosis, motor impairment ↑ expression of GDNF, dopamine levels	Yuan et al. (2017)
			DA-JC4/DA-CH5	In-vivo 60 adult male C57BL/ 6 mice, 8 weeks old, 15–20 g	25 nmol/kg, i.p. route	6 days	↓ proinflammatory cytokines, glial activation, motor impairment ↑ GDNF expression, dopamine synthesis	Feng et al. (2018)
			DA-JC1	In-vivo 24 male Sprague Dawley rats, 350–450 g	25 nmol/kg, i.p. route	42 days	↑ GDNF expression ↓ dopaminergic neuronal loss	Jalewa et al. (2017)
			DA -JC4	In-vivo adult male Sprague -Dawley rats, 230 − 280 g	50 nmol/kg, i.p. route	7 days	↓ cell death, mitochondrial stress	T. Li et al. (2020); Y. Li et al. (2020)
3	Huntington's disease	↓ IGF-1	Rutin	In-vivo 100 C. elegans strains HA759, AM141, Bristol N2 (wild-type), TJ356, DA2123	15, 30, 60 and 120 μM (9.16–73.26 mg rutin/ml agar)	120 h	↑ lifespan of C. elegans ↓ ROS levels, PolyQ aggregation, autophagy	Cordeiro et al. (2020)
			IGF-1	In-vitro Striatal cell lines STHdhQ7/Q7 STHdhQ111/Q111	0.1–10 nM	24 h	↓ mitochondrial ROS, apoptosis	Ribeiro et al. (2014)

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S. No.	Disease	Target involved	Target activator	Study type/species/ gender/age weight/ no. of species	Dose/Route	Study duration	Key findings	References
			rhIGF-1	In-vivo 32–36 male HD transgenic YAC128 mice & non-transgenic mice, 6 months old, 28–45 g	35 µl, i.n. route	14 days	↑ IGF-1 cortical levels, pyruvate levels ↓ Energy Deficits Improved motor function	Lopes et al. (2014)
			Mn^{+2} +IGF-1	In-vitro WT Q7/ Q7 STHdh cells and STHdh Q111/Q111 HD cell	IGF-1 (1–10 nM), Mn^{+2} (50–500-µM), Mn^{+2} 200 µM	3 h	↓ glucose uptake ↑ Akt activity	Bryan et al. (2020)
			recombinant human IGF-1	In-vivo 22 WT and 20 R6/2 male mice, 9 week-old	50 µg/kg infusion rate 0.25 µl/h), s.c. route	14 days	↑ blood insulin levels, IGF-1 levels	Duarte et al. (2011)
			Cannabigerol	In-vivo 24–32 C57BL/6 male mice, 16 weeks old, 18–20 g	10 mg/kg, i.p. route	70 days	↓ Reactive microgliosis, motor deficits ↑ gene expression for BDNF, IGF-1, PPARγ	Valdeolivas et al. (2015)
		↓ GLP-1	Liraglutide + Ghrelin	In-vivo 10 week old R6/2 mice	Liraglutide-0.2 mg/kg, Ghrelin-150 µg/kg, s.c. route	14 days	↓ brain insulin, lactate, AMP, cholesterol levels	Duarte et al. (2018)
			Exendin-4 + GLP-1 Tf	In-vivo Male B6C3-Tg (HD82Gln)81Dbo/J (N171– 82Q) mice, 2 months, 20–25 g	Exendin-4 - 10, 300 µl of 0.1 µmol/L, GLP-1 Tf- 10, 1 mg/kg, s.c. route	35 days	improved pancreatic morphology and motor coordination	Martin et al. (2012)
			Vildagliptin	In-vivo 70 Adult male, Wistar albino rats, 180 ± 20 g	5 mg/kg, p.o. route	14 days	↑ GLP-1 levels, cognitive	Sayed et al. (2020)
4	Traumatic brain injury	↓ IGF-1	recombinant human IGF-1 (rhIGF)	In-vivo Adult male C57BL/ 6 J mice, 8–10 weeks, 25–30 g	10 µg, i.c.v. infusion	7 days	↑ hippocampal neurogenesis ↑ IGF-1 level in brain that promotes neurobehavioral recovery after TBI	Carlson and Saatman (2018)
			cDNA of human IGF-1 vector (RAd-IGF1)	In-vivo Male Wistar rats, 3–4 months, 250–330 g	10^{10} plaque forming units (pfu), i.m. route	7 days	↓ reactive microglia in the cerebral cortex	Herrera et al. (2021)
			Recombinant annexin A2	In-vivo AXNA2 knock-out mice, In-vitro Isolated Cerebral Microvascular Fragments and Brain Tissues	1 mg/kg, i.p. route	7 days	↑ IGF-1, VEGF, BDNF, eNOS, Tie2 mRNA, ang1, cerebral angiogenesis activated Akt, ERK, and CREB	Cheng et al. (2021)
			hIGF-1 biotinylated human IGF-I	In-vivo Adult male C56BL/6, 28–35 g, liver IGF-I deficient (LID) mice	50 µg/kg, s.c. route 150 µg/kg, i.p. route	28 days 7 days	↑ IGF-I levels in brain after injury	Santi et al. (2018)
		↓ GLP-1	Exendin-4	In-vivo 78 Adult male Sprague Dawley rats, 200–250 g	10 µg/kg/d Tail vein injection	21 days	↓ TNFα and IL-1β overexpression ↑ cerebral blood flow recovery and cognitive ability	Zhang et al. (2020)
				In-vivo Male mice, 30–40 g	21 µg/kg/day s.c. route	30 days	↑ cognitive deficits	Rachmany et al. (2017)
				In-vivo Male ICR mice, 30–40 g	21 mg/kg/day s.c. route	14 days	↓ memory deficits, neurodeneration	Tweedie et al. (2016)
				In-vivo Male Sprague-Dawley rats, 350–400 g	21.1 µg/kg/day s.c. route	14 days	↓ cognitive impairments	Eakin et al. (2013)
				In-vitro rat cerebral cortical	100 nM and 1 µM	1 h		Eakin et al. (2013)

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S. No.	Disease	Target involved	Target activator	Study type/species/ gender/age weight/ no. of species	Dose/Route	Study duration	Key findings	References
				neurons and Human SH-SY5Y neuroblastoma cells			↓ caspase-3 activity, apoptosis, cAMP, cell viability	
				In-vivo male ICR mice, 30–40 g	21 mg/kg/day s.c. route	30 days	↓ behavioral sequelae of mTBI	Rachmany et al. (2013)
				In-vitro rat cerebral cortical neurons and Human SH-SY5Y neuroblastoma cells	100 nM		↑ neuroprotection ↓ H2O2-induced oxidative stress, glutamate toxicity	Rachmany et al. (2013)
				In-vivo 65 Male ICR mice, 30–40 g	3.5 pM/kg/min s.c. route	14 days	↓ behavioral deficits	Tweedie et al. (2013)
			Liraglutide+ twincretin	In-vivo Adult ICR mice, 6–8 weeks, 31–34 g	Liraglutide: 246.7 μg/kg Twincretin: 50 μg/kg s.c. route	30 days	↑ PKA phosphorylation levels ↓ microglial expression, Neurodegeneration, cognitive deficits	Bader et al. (2020)
			Liraglutide	In-vivo 79 Adult male Sprague, 300–400 g	75 μg/kg 200 μg/kg, s.c. route	7 days	↓ cerebral edema in pericontusional regions, cortical tissue loss	Hakon et al. (2015)
				In-vitro SH-SY5Y cells Primary cortical rat neurons	1 μM	24 h	↑ Cell viability, dose-dependent proliferation ↓ oxidative stress, glutamate excitotoxicity-induced cell death	Li et al. (2015)
				In-vivo Male ICR mice, 30–40 g	246.7 μg/kg/day, s.c. route	7 days	↓ memory impairments	Li et al. (2015)
				In-vivo Female C57Bl6/j mice, 7–12 weeks old, 18.9 g	200 μg/kg, s.c. route 75 mg/kg, i.p route	4 days	↓ lesion size, ROS production, Necrosis, Apoptosis, CREB activation	DellaValle et al. (2014)
			Sitagliptin	In-vivo Female C57Bl6/j mice, 6–8 weeks old	50 mg/kg, Oral route	2 days	↓ lesion size ↑ manganese superoxide dismutase, cAMP	DellaValle et al. (2016)
			Clostridium butyricum	In-vivo Male C57BL/6 mice, 6–8 weeks old, 18–22 g	10^9 CFU/ml, i.g. route	14 days	↓ Bax, brain edema, BBB impairment, ↑ Bcl-2, p-Akt, intestinal GLP-1 secretion, cerebral GLP-1R expression	Li et al. (2018)
			PT302 (sustained-release formulation of Exenatide)	In-vivo male ICR mice, 30–40 g, adult male Sprague-Dawley rats, 2 months old	0.024 mg/kg, 0.12 mg/kg, 0.6 mg/kg, s.c. route	7 days	↓ cognitive impairments, neuronal loss, neuroinflammation	Bader et al. (2019)
			Triagonist (GLP −1R/GIPR/GcgR)	In-vivo Male ICR mice 6–8 weeks old, 30–40 g In-vitro Immortal SH -SY5Y human neuroblastoma cell line, Mouse primary astrocyte	50 μg/kg, s.c. route 10 nM (10^{-8} M)	7 days 1 h	↓ Visual and spatial memory deficits ↑cyclic AMP levels ↓Oxidative stress, Glutamate excitotoxicity	T. Li et al. (2020); Y. Li et al. (2020)
			Human GIP	In-vivo Adult male Sprague-Dawley (SD) rats, 250–300 g	21.58 μg/kg/day, 38.85 μg/kg/day, s.c. route	14 days	↓ spatial memory loss, recognition memory impairments, BMX levels, GFAP and APP	Yu et al. (2016)
5	Ischemia and stroke	↓ IGF-1	IGF-1	In-vivo Male Sprague-Dawley rats, 4–6 weeks old, 200–250 g	0, 4, 6, and 8 μg, i.v. route	14 days	↑ IGF-1 levels in plasma, cortex, hippocampus, amygdala ↓ tau phosphorylation in hippocampus, IL-1β, IL-6, TNF-α, brain edema, cerebral infarction, cognitive deficits	Yang et al. (2020)
				In-vivo 61 female Sprague	100 mg/ml, ICV route	24 h		Bake et al. (2014)

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S. No.	Disease	Target involved	Target activator	Study type/species/ gender/age weight/ no. of species	Dose/Route	Study duration	Key findings	References
				Dawley rats 9–11 months old 325–350 g			↑ Phospho-Akt ↓ blood brain barrier permeability	
			human recombinant (rh) IGF-1	In-vivo 55 Female Sprague Dawley (SD) rats, 10–12 months old, 325–350 g	100 μg/ml, ICV route	5 days	↑ stroke recovery, behavioral improvements ↓ infarct volumes	Bake et al. (2019)
				In-vitro Human brain microvascular endothelial cells (hBMEC)	10 ng/ml	6 h	↑ cell-cell interaction preserved endothelial monolayer	Bake et al. (2019)
				In-vivo Sprague-Dawley rats, 7 days old, 13–19 g	50 μg, i.n. route	2 days	↓ infiltration of polymorphonuclear leukocytes, activation of microglia, NF-κB activation	Lin et al. (2011)
				In-vivo Male albino Wistar rats, 6–8 weeks old, 275–300 g	300 μg, s.c. route	72 h	↓ iNOS transcripts in microglia, infarct volume, level of Iba-1 ↑ sensorimotor function, mRNA expression of TGF-β	Serhan et al. (2020)
			AAV5-GFAP-hIGF-1	In-vivo Female Sprague Dawley (SD) rats, 10–12 months old, 325–350 g	2.5 31011 viral particles (VP)/ml (low dose) 2.5 3 1012 (VP)/ml (high dose)	7 days	↓ GFAP circulating serum levels improved blood pressure	Okoreeh et al. (2017)
		↓ GLP-1	GLP-1 (9–36)	In-vivo GLP-1 receptor knockout (Glp-1rKO) mice, 8–10 weeks old	250, 500, and 1000 ng/g/day, i.p. route	7 days	↓ infarct volume, astrogliosis, neuronal apoptosis, IL-6 levels, IL-1β, TNF –α	Huang et al. (2020)
			Exendin-4	Ex-vivo 39 male Sprague–Dawley rats, 220–250 g	10 μg kg^{-1}, i.v. route	24 h	reversed arteriolar constrictions ↑ brain tissue PO2, cerebral blood fow	Nizari et al. (2021)
			6,7-dichloro-2-methylsulfonyl-3-N-tert-butylaminoquinoxaline (DMB)	In-vivo Adult male C57BL/6 mice, 18–22 g	5 μmol/kg, Oral route	120 min	↑ cAMP levels ↓ Necrosis, apoptosis cell death, cerebral infarct size	Zhang et al. (2016)
6	Depression	↓ IGF-1	PEG-IGF-1	In-vivo 35 male C57BL/6 J mice, 4 weeks old	1 mg/kg, i.p. route	84 days	↓inflammation and, oxidative stress, mitochondrial deficits	Yang et al. (2021)
			IGF-1	In-vivo 18 adult male Sprague Dawley rats, 250–275 g	0, 1, 5, 10 μg, ICV route		↑ Neuroplasticity ↓ insulin or IGF-1 sensitivity	Mueller et al. (2018)
				In-vitro hippocampal slice cultures	40 or 100 ng/ml	7 days	↓ SD susceptibility, Hyperexcitability ↑ endogenous antioxidants	Grinberg et al. (2012)
			human recombinant IGF-1	In-vivo 109 Adult male Wistar rats, 214–414 g	150 μg/50 μl, i.n. route	14 days	↓ SD susceptibility	Grinberg et al. (2017)
		↓ GLP-1	Lixisenatide	In-vivo male C57BL/6 N mice, 8 weeks old	10 nmol/kg, 50 nmol/kg, i.n. route	40 days	↓ depressive and anxiety behaviors ↑ neurogenesis, phosphorylation of CREB protein	Ren et al. (2021)
			Liraglutide	In-vivo 60 Adult male C57BL/6 N mice, 8 weeks old	5, 20 nmol/kg, i.p. route	30 days	↑level of phosphorylated GSK3β, cell density of immature neurons ↓ stress hormone induced hyperactivity	Weina et al. (2018)
			Exendin-4	In-vivo 48 male Wistar rats, 200 g	0.5 μg/kg, i.p. route	5 days	↓ depressive-like symptoms	Ventorp et al. (2017)
7	Autism	↓ IGF-1	human insulin-like growth factor 1 (IGF-1)	In-vivo C57BL/6, 3 months old	120 μg/kg/day 240 μg/kg/day, i.p. route	14 days	↑ motor performance, long-term potentiation (LTP), AMPA signaling	Bozdagi et al. (2013)
		↓ GLP-1	Exenatide	In-vivo 16 female and 6 male Sprague–Dawley	20 μgr kg^{-1} day^{-1}, i.p. route	45 days	↓ inflammation, oxidative stress, hippocampal gliosis	Solmaz et al. (2020)

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S. No.	Disease	Target involved	Target activator	Study type/species/ gender/age weight/ no. of species	Dose/Route	Study duration	Key findings	References
				adult rats, 238 ± 10 g				
8.	Schizophrenia	↓ GLP-1	Liraglutide	In-vivo 24 male Swiss albino mice, 20–25 g	50 μg/kg, i.p. route	1 h	Attenuated apomorphine-induced climbing behavior	Dixit et al. (2013)
9.	Amyotropic lateral sclerosis	↓ IGF-1 and GLP-1	4-hydroxyisoleucine	In-vivo 36 wistar rats, 6 months old, 250–300 g, male and female	50 mg/kg and 100 mg/kg Oral route	42 days	↑ IGF-1 and GLP-1 ↓ inflammation, oxidative stress	Shandilya et al. (2022)
		↓ IGF-1	AAV-IGF-1 vectors	In vivo 100 transgenic mice 88–90 months old	Stereotaxic injection	20 days	Delayed ALS progression	Dodge et al. (2008)

The table enlists the neurological diseases/disorders in which IGF-1/GLP-1 receptors have been down regulated. The involvement of IGF-1/GLP-1 receptor agonists have been enumerated with preclinical evidences in the variety of neurological disorders. The type of study with the age, gender and number of animal species used in the respective study has been mentioned. The dose and route of the activators along with the duration of study involving IGF-1/GLP-1 receptor activators have been added. The main highlight of the table is key findings which includes the outcomes of the respective preclinical evidences that are mentioned.

4.3. Huntington's disease (HD)

HD is an entirely penetrant neurological disorder caused by a dominant CAG trinucleotide repeat increase in the huntingtin gene on chromosome 4 (McColgan and Tabrizi, 2018). It is often characterized by varied symptoms and neuropathology of the basal ganglia and cortex associated with progressive corticostriatal circuit malfunction and neuronal death (Mehrabi et al., 2016; Carroll et al., 2015). The symptoms include motor dysfunctions, cognitive impairment, and mental and behavioral abnormalities (Wyant et al., 2017). While HD is a late-onset neurodegenerative disease, both rodent research and neuroimaging studies of presymptomatic mutation carriers imply that HD may impact neurodevelopment (Barnat et al., 2020).

IGF-1 is critical in activating signaling pathways and improving mitochondrial and metabolic function in HD human lymphoblasts (Naia et al., 2015). IGF-1 has been demonstrated to enhance ATP and decrease cytochrome C levels in lymphoblastoid cell lines in HD patients (Naia et al., 2015). Additionally, recombinant human IGF-1 has been shown in numerous in vivo investigations to increase IGF-1 cortical levels, reducing mitochondrial stress and apoptosis (Lopes et al., 2014; Duarte et al., 2011). Rutin and cannabigerol reduce reactive microgliosis and reactive oxygen species (ROS) levels, leading to improved motor impairments (Cordeiro et al., 2020; Valdeolivas et al., 2015).

GLP-1 receptor analogues have been reported to alleviate the pathology and symptoms of HD in various preclinical and clinical studies. In clinical trials, Liraglutide, a GLP-1 analog, has been shown to possess neuroprotective effects in HD by restoring defective insulin signaling, increasing autophagy, and decreasing oxidative stress (Chang et al., 2018). Additionally, various in vivo investigations using GLP-1 activators have demonstrated potential efficacy in preventing neurological dysfunctions associated with HD. In combination with ghrelin, liraglutide reduces brain insulin, lactate, AMP, and cholesterol levels (Duarte et al., 2018). Exendin-4 has been shown to improve the pancreas' morphology and motor coordination (Martin et al., 2012). Vildagliptin, a DPP-4 inhibitor, improved GLP-1 levels, leading to enhanced cognitive and motor impairments (Sayed et al., 2020). Lastly, IGF-1 and GLP-1 mimetics have a wide range of protective effects on the neuropathological processes involved in HD. These findings suggest that these drugs could be employed as potential HD therapeutics.

4.4. Autism spectrum disorder (ASD)

ASD is associated with a group of debilitating brain disorders in childhood (Sharma and Mehan, 2021). ASDs are classified into five PDDs in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition – Text Revision (DSM-IV-TR), including autistic disorder, Asperger syndrome, PDDs not otherwise specified, and Rett syndrome (RTT), and childhood disintegrative disorder (Wiggins et al., 2019). However, these classifications are collectively referred to as ASD in the recently published DSM-V. Numerous morphological and cellular abnormalities including microcephaly, macrocephaly, increased cell density, increased brain weight or size, decreased neuronal size in the autistic limbic system, decreased Purkinje cell number in the cerebellum, small and pale neurons in the brainstem, and cortical dysgenesis. Lastly, migration abnormalities have been reported in the brains of patients with ASDs (Fombonne et al., 1999). Current theories of ASD have emphasized the disorder's underlying dysfunction comprises improper temporal synchronization of brain activity in cortical circuits. Sun and co-workers demonstrated that poor gamma-band activity contributes to complex visual processing in ASD, implying an unusual modulation of high-frequency power in front posterior networks (Sun et al., 2012). It has been reported that the haploinsufficiency of the autism-associated CHD8 gene inhibits cortical neurons' axon growth and migration (Xu et al., 2018). In preclinical and clinical studies, autism-associated Nf-1 loss has been shown to alter corticocortical and corticostriatal functional connections (Shofty et al., 2019). According to a research study, an imbalance of oxidants and antioxidants in the cerebellum increases oxidative stress and is directly associated with autism-like behavior in BTBR mice (Nadeem et al., 2019). Recently, it has been discovered that Pianp deficiency is connected with cerebellar abnormalities and Purkinje cell destruction, both of which contribute to autism-like behavior (Winkler et al., 2020). These patients exhibit social-communicative deficits, such as a lack of nonverbal communication skills, inability to develop and sustain relationships, repetitive behaviors, and varying degrees of cognitive impairment (Evers et al., 2021). Numerous studies on autistic patients and preclinical models indicate that IGF-1 and GLP-1 activators effectively treat and prevent neuropathological conditions associated with autism.

The IGF-I/PI3K/AKT/mTOR pathway has been implicated in several molecular cascades underlying ASDs (Kwon et al., 2006; Bozdagi et al., 2013). According to clinical research, fluoxetine increases IGF-1 levels in CSF while decreasing DAT binding (Makkonen et al., 2011). Linker et al. revealed that the response to recombinant human IGF-1 was diverse in neurons derived from ASD patients, and the synapse genes were recovered (Linker et al., 2020). Because autism is a spectrum condition, it encompasses various syndromes, such as Rett syndrome. IGF-1 (Mecasermin-Increlex) is well tolerated by people with Rett syndrome (Pini et al., 2012, 2016; Khwaja et al., 2014). Torfenatide also

Table 2
Involvement of IGF-1 and GLP-1 receptor activators in various neurological diseases with clinical evidences.

S. No.	Disease	Target involved	Target activator	Target dose/ route	Study design/patient population/age /gender	Clinical trial status/ uration of study	Location	Key findings	References
1.	Alzheimer's Disease	↓ IGF-1	GHRH analog (IGF-1 inducer)	1 mg/day, s.c. route	Interventional, randomized, double blinded study, 152 older adult patients, 55 years, gender 90 males and females	Completed, 20 weeks	University of Washington Seattle, Washington, United States	↑ Cognitive function, Serum IGF-1 levels	Friedman et al. (2013), Baker et al. (2012)
			IGF-1	50, 100, 200 and 400 ng/ml	In-vitro human neuroblastoma cell line SHSY5Y	24 h	Department of Senile Neurology, Shandong UniversityJinan, China	↓ Aβ25–35-induced cell death	Hou et al. (2017)
		↓ GLP-1	Liraglutide	0.6 mg, 1.2 mg, 1.8 mg, s.c. route	multi-centre, randomised, double-blind, placebo-controlled, phase IIb trial, 206 patients, 50 years old	Completed 48 weeks	Department of Medicine, Imperial College London, London, UK	↑ cerebral glucose in the cortex ↓ Levels of cortical amyloid load.	Femminella et al. (2019)
				0.6 mg, 1.2 mg, 1.8 mg, s.c. route	Randomized, placebo-controlled, double blind controlled clinical trial 38 patients, 50–80 years, gender 21 males, 13 females	Completed 24 weeks	Institute of Biomedicine, Aarhus University, Aarhus, Denmark	↑ Glucose metabolic rate, Cognitive capabilities ↓ Aβ deposition	Gejl et al. (2016)
				10–200 nM	In-vitro human neuroblastoma cell line SH-SY5Y	24 h	Fujian Institute of Endocrinology, Union Hospital of Fujian Medical University, Fuzhou, People's Republic of China	↓ apoptosis, autophagy and cellular cytotoxicity	Liu et al. (2016)
2.	Parkinson's disease	↓ IGF-1	Blackcurrant Anthocyanins	300 mg, Oral route	Pilot study, 11 male patients, 40 years old	Completed 4 weeks	Department of Pharmacology and Clinical Pharmacology, University of Auckland, Auckland	↑ CSF cGP	Fan et al. (2018)
			Vitexin + IGF-1	Vitexin conc. 10, 20, and 40 μM, IGF-1 conc. 50 ng/ml	In-vitro Human neuroblastoma SH-SY5Y cells	24 h	Department of Neurology, Shenzhen Hospital, Southern Medical University, Shenzhen, Guangdong, China	↑ cell viability ↓ cell apoptosis, caspase-3 activity, Bax/Bcl-2 ratio	Hu et al. (2018)
			NAC+IGF-1	NAC 3 mM, IGF-1 20 nM	In-vitro Human SH-SY5Y cells	18 h	Regional Academic Health Center, School of Medicine, University of Texas Rio Grande Valley, Edinburg, TX, USA	↑ cell viability ↓ apoptosis, ROS, endoplasmic reticulum stress	Cheng et al. (2016)
		↓ GLP-1	Exenatide	2 mg, s.c. route	single-centre, randomised, double-blind, placebo-controlled trial, 62 patients, 25–75 years, 44 male and 16 female	Recruiting (Phase 3) 48 weeks	University College London Hospital London, United Kingdom	• higher baseline MDS-UPDRS part 3 scores	Athauda et al. (2017)
				5 μg 10 μg, s.c. route	single-blind trial design, 45 patients, 45 and 70, 35 males 20 females	16 weeks	National Hospital for Neurology and NeurosurgeryLondon, United Kingdom	• improvement in motor and cognitive measures	Aviles-Olmos et al. (2013)
				10 ug, s.c. route	open label, proof of concept trial 44 patients, 59–61 years,	96 weeks	University College London HospitalLondon, United Kingdom	Improved MDS-UPDRS part 3 motor subscale	Aviles-Olmos et al. (2015)
3.	Huntington's disease	↓ IGF-1	IGF-1	0.1 nM	In-vitro Human lymphoblastoid cell	24 h	Center for Neuroscience and Cell Biology, University of Coimbra, Coimbra, Portugal	↑ ATP, phosphocreatine ↓ lactate, levels of cytochrome C	Naia et al. (2015)

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Table 2 (*continued*)

S. No.	Disease	Target involved	Target activator	Target dose/ route	Study design/patient population/age /gender	Clinical trial status/ uration of study	Location	Key findings	References
					lines (4 males & 1 female HD patients and 3 males and 1 female control)				
		↓ GLP-1	Liraglutide	0.1 μM	In-vitro Human neuroblastoma SK-N-MC cells	Completed 48 h	Chung Shan Medical University Hospital, Taiwan	↑ autophagy ↓ oxidative stress	Chang et al. (2018)
4.	Autism	↓ IGF-1	Fluoxetin	10–40 mg (0.4–0.9 mg/ kg), Oral route	Cohort study, 13 autistic patients, 5–16 years old, 12 males and 1 female	Completed 24 weeks	Department of Pediatrics, Unit of Child Neurology, Kuopio University Hospital, Kuopio, Finland	↓ DAT binding in striatum ↑ IGF-1 levels in CSF	Makkonen et al. (2011)
			recombinant human (rh) IGF-1	20 ng/ml	In vitro pluripotent stem cells (iPSC) from neurotypical controls and idiopathic ASD individuals	37 days	The Salk Institute, Laboratory of Genetics, La Jolla, CA, USA	Heterogeneous response to IGF-1 treatment in neurons derived from ASD patients Synapse genes recovered	Linker et al. (2020)
a.	Rett syndrome	↓ IGF-1	IGF1 (Mecasermin-Increlex)	0.05 mg/kg-0.1 mg/kg, s.c. route	Pilot study, 6 females patients, between 4 and 11years,	Completed 24 weeks	Tuscany Rett Center, Versilia Hospital, Lido di Camaiore, Italy	↑ IGF1 tolerance	Pini et al. (2012)
				0.05–0.1 mg/ kg, s.c. route	Pilot study, 10 females patients, 2–13 years old,	Completed 20–24 weeks	Tuscany Rett Center, Versilia Hospital, Lido di Camaiore, Italy	Improvement in International Scoring System	Pini et al. (2016)
			Trofinetide	50 mg/kg, 100 mg/kg, 200 mg/kg, Oral route	phase 2, multicenter, double-blind, placebo-controlled, parallel-group study, 82 patients, age 5–15 years, gender females	Completed 42 days	Department of Pediatrics and Neurology (D.G.G.), Baylor College of Medicine, Houston, TX; Department of Neurosciences (J.L.N.), University of California, San Diego	Improved Clinical Global Impression Scale, RTT-Clinician Visual Analog Scale and Behaviour Questionnaire	Glaze et al. (2019)
			Mecasermin	40 μg/kg, 80 μg/kg, 120 μg/kg, s.c. route	Multiple ascending dose (MAD) study followed by open-label extension (OLE) period, 12 females Patients, 3–10 years old	Completed 4 weeks	Department of Neurology, Boston Children's Hospital and Harvard Medical School, Boston, MA	↑ brain IGF-1 levels	Khwaja et al. (2014)
		↓GLP-1	Liraglutide	0.6 mg, 2.4 mg, s.c. route	Case report, Single patient, age 20 years, gender Male	Completed 36 weeks	Department of Psychiatry, University of Helsinki, Helsinki, Finland,	Improvement in food-related compulsive behavior	Järvinen et al. (2019)
5.	Schizophrenia	↓ IGF-1	Risperidone Olanzapine Flupenthixol	4.9 ± 1.6 mg/ day, oral route 10.2 ± 1.5 mg/ day, oral route 20 mg, i.m. depot injection	longitudinal study, 33 patients, 33.8 ± 8.2 years, 20 men	Completed 12 weeks	Department of Psychiatry, National Institute of Mental Health and Neurosciences, Bangalore India	↑ IGF-1 levels ↓ cortisol levels	Venkatasubramanian et al. (2010)
			Clozapine	300 mg, orally	randomized, controlled study, 53 patients, 18–65 years, 11males 14 females	Completed 24 weeks	Yu Li Veterans Hospital, Hualien, Taiwan	↑ molar ratio of IGF-1 to IGFBP-3 ↓ BMI, body weight, insulin, IGFBP-3 levels, triglyceride,	Wu et al. (2007)
			Insulin IGF-1 BDNF	200 nmol/L 1.53 nmol/L 7.5 nmol/L	In-vitro human SH-SY5Y	Completed 3 days	Uniformed Services University Health Sciences Bethesda, Maryland	↑ genes expression involved in glucose and energy metabolism, hydrogen ion transport,	Altar et al. (2008)

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Table 2 (*continued*)

S. No.	Disease	Target involved	Target activator	Target dose/ route	Study design/patient population/age /gender	Clinical trial status/ uration of study	Location	Key findings	References
					neuroblastoma and astrocyte cell lines			mitochondrial functions, and synaptic function	
		↓ GLP-1	liraglutide, exenatide, exenatide-LAR	0.3–0.9 mg, 10 or 20 ug, 2 mg	prospective non-randomized study, 7 patients, less than 18 years old, males and females	Completed 1 year	Koseikai Michinoo Hospital, Nagasaki, Japan	Improved HbA1c	Ando et al. (2018)
			Exenatide	2 mg, s.c. route	open-label, parallel, randomised, controlled pilot trial, 28 outpatients, 18–64 years old, 18 males	Completed, 24 weeks	Metro South Addiction and Mental Health Service, Brisbane, Australia	↑ mean weight loss, ↓ BMI, fasting glucose	Siskind et al. (2018)
				2 mg, s.c. route	randomized, placebo-controlled, double-blinded, parallel group trial, 40 patients, 18 and 65 years old 20 males and 20 females	Completed, 12 weeks	Cnsr/CinsGlostrup, Denmark	↑ weight loss ↓ BMI	Ishøy et al. (2017)
				2 mg, s.c. route	open-label, pilot randomised controlled trial, 60 patients, 18–64 years old, males or females	Completed, 24 weeks	Metro South Addiction and Mental Health Service, Brisbane, Australia	↑ glycaemic control ↓ HbA1c	Mayfield et al. (2015)
				2 mg, s.c. route	randomised, placebo-controlled, double-blinded trial, 40 patients, 18 and 65 years	Completed, 12 weeks	Cnsr/CinsGlostrup, Denmark	↑ weight loss ↓ BMI	Ishøy et al. (2014)
6.	Stroke	↓ IGF-1	Aspirin + dipyridamol ER	Aspirin 25 mg, Dipyridamol 200 mg	Interventional trial, 404 patients, 67 ± 11 years, 143 females	Completed, 13 weeks	Boehringer Ingelheim Investigational Site, Bad Homburg, Germany	↑IGF-1 levels ↓ IGFBP-3 levels	Armbrust et al. (2017)
		↓ GLP-1	Exenatide	5 ug, s.c. route	Phase 2, multi-center, prospective, randomized, open label, blinded end-point trial, 528 patients Age > 18 years	Ongoing, 3 years	St Vincent's Hospital SydneyDarlinghurst, New South Wales, Australia	↓ Post stroke hyperglycemia	Muller et al. (2018)
				10 μg, s.c. route	Randomized controlled trial, 19 male patients, 70–80 years old, 9	24 h	Department of Clinical Science and Education at Södersjukhuset, Karolinska Institutet, Stockholm, Sweden	↓ plasma glucose	Larsson et al. (2019)
7.	TBI	↓ IGF-1	rhGH	400 μg/day, s.c. route	Phase IIa, randomized, double-blind, placebo, controlled trial, 40 male patients, 16–65 years old,	Completed, 24 weeks	Department of Physical Medicine and Rehabilitation, Baylor Institute for Rehabilitation, Dallas, TX, United States	↑ IGF-1 levels	Dubiel et al. (2018)
			IGF-I/GH	0.01 mg/kg/hr, i.v. infusion,	prospective, randomized, double-blind study, 97 patients,	Completed, 72 h	Colleges of Pharmacy, Public Health, and Medicine, University of Kentucky, Lexington, Kentucky	↑ IGF-1 levels	Hatton et al. (2006)

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Table 2 (*continued*)

S. No.	Disease	Target involved	Target activator	Target dose/ route	Study design/patient population/age /gender	Clinical trial status/ uration of study	Location	Key findings	References
				0.05 mg/kg, s.c. route	18–59 years old, 71 male and 26 females				
8.	Amyotropic lateral sclerosis	↓IGF-1	IGF-1	0.5 and 3 μg/kg, Intrathecal route	double-blind clinical trial, 9 patients, 20–70 years old	Completed, 40 weeks	Department of Neurology, Graduate School of Medicine and Dentistry, Okayama University, Japan	↑ motor functions in ALS	Nagano et al. (2005)

The table enumerates the neurological diseases in which IGF-1/GLP-1 receptors have been down regulated. The involvement of IGF-1/GLP-1 receptor agonists have been depicted with clinical evidences in the variety of neurological disorders. The dose and route of the activators has been mentioned along with the type of clinical study they are involved in. Number of patients involved with their age and gender is also listed. Status of clinical trial and duration of study involving IGF-1/GLP-1 receptor activators have been added. The main highlight of the table is key findings which contains the outcomes of the respective clinical evidences that are mentioned.

improves the behaviour scores of patients with Rett syndrome, ultimately abolishing the RTT symptoms (Glaze et al., 2019). IGF-1 restored hippocampus AMPA signaling impairments, enhancing long-term potentiation and motor coordination (Bozdagi et al., 2013).

GLP-1 and its receptor equivalents have been explored clinically and preclinically to treat autistic-like behavior and neuropathological diseases. Liraglutide, a well-known GLP-1 receptor activator, has significantly reduced food-related obsessive behavior in a single autistic patient (Järvinen et al., 2019). In a preclinical study, exenatide has also been shown to reduce oxidative stress, inflammation, and hippocampus gliosis (Solmaz et al., 2020). The above clinical and preclinical investigations conclude that IGF-1 and GLP-1 agonists reversed mechanistic abnormalities in ASD, leading to positive effects on neuropsychiatric and behavioural factors.

4.5. *Schizophrenia*

Schizophrenia is a chronic, heterogeneous, multifaceted, and debilitating condition caused by complex genetic, epigenetic, developmental, and environmental variables that impair normal brain development and maturation (Insel, 2010). It has been suggested that dysregulation of the immune system, specifically a lack of Toll-like receptors, contributes to the aetiology of neuropsychiatric diseases such as schizophrenia (Park et al., 2015). Preclinical research was driven by the evidence linking thalamocortical oscillations to the neuropathophysiology of schizophrenia in mice and humans (Czekus et al., 2021). It has been suggested that a deficit in the excitatory drive to parvalbumin-containing cortical interneurons serves as a critical neural substrate for abnormal gamma oscillations and cognitive impairment in schizophrenia (Chung et al., 2016). On a cellular level, a substantial increase in microglia density has also been observed in people with schizophrenia (Van Kesteren et al., 2017). Schizophrenia is characterized by positive, negative, and cognitive symptoms. Positive symptoms include psychotic manifestations such as delusions and hallucinations. In contrast, negative symptoms (NS) include deprivation of thoughts and altered actions, a lack of drive, dulled effect, significant social withdrawal, and a deficiency of speech and communication. Finally, cognitive symptoms include memory, attention difficulties, and executive functioning disorders (Cerveri et al., 2019).

IGF-1 has demonstrated potential benefits in eradicating schizophrenia symptoms via increasing IGF-1 levels. In a longitudinal clinical investigation of thirty-three individuals with schizophrenia, triple therapy of risperidone, olanzapine, and flupenthixol increased IGF-1 levels and decreased cortisol levels (Venkatasubramanian et al., 2010). In a randomized controlled clinical trial of clozapine on schizophrenia patients, the IGF-1 to IGFBP3 molar ratio increased remarkably (Wu et al., 2007). Insulin, IGF-1, and BDNF induce the expression of genes involved in mitochondrial activity, glucose, energy metabolism, hydrogen ion transport, and synaptic function in vitro (Altar et al., 2008). Preclinical research on the IGF-1 protective activity in schizophrenia is of the utmost need.

GLP-1 analogues such as Liraglutide, exenatide, and exenatide-LAR in seven individuals with schizophrenia improved HbA1c levels (Ando et al., 2018). Exenatide has been demonstrated in numerous clinical studies to promote weight loss and BMI reduction, and lower Hba1c levels, hence improving glycemic control in schizophrenia (Siskind et al., 2018, 2015). Additionally, Liraglutide has been shown to reduce the climbing behavior induced by apomorphine in a mouse model of schizophrenia (Dixit et al., 2013). Finally, the above-cited studies demonstrate the neuroprotective benefits of IGF-1 and GLP-1 activators in schizophrenia. Still, the data supporting the effects of IGF-1 and GLP-1 agonists in schizophrenia is insufficient. In conclusion, more research could confirm the protective neuropsychiatric effects of IGF-1 and GLP-1 agonists in schizophrenia.

4.6. Cerebral ischemic stroke

A stroke is a cerebrovascular accident that can be ischemic, hemorrhagic, or subarachnoid. Ischemic stroke occurs due to a thrombotic or embolic event causing a reduction in blood flow to the brain (Hui et al., 2018). Cerebral ischemia is classified into localized and global ischemia (Lee et al., 2018). Hemorrhagic strokes and ischemic strokes are both types of brain strokes. 20 % of CVAs result from a hemorrhagic stroke caused by a ruptured blood vessel and 80 % by occlusion or obstruction of brain arteries (Cahlin, 2021). The neuropathology of cerebral ischemia includes hippocampal damage, decreased cerebral blood flow, lesions in white matter, cytotoxic edema, cholinergic dysfunction, calcium overload, excitotoxicity, neuronal cell death, dysfunctional Na+ / K+ -ATPase, a decrease in adenosine triphosphate (ATP), and a breakdown of the blood-brain barrier (Ahad et al., 2020). Ischemic stroke manifests in various ways, including vomiting, ataxia, paresis, paralysis, and altered eye gaze; however, the location of these symptoms depends on the brain areas nourished by suffering vessels (Ojaghihaghighi et al., 2017). Recent studies indicate that IGF-1 and GLP-1 analogues may be helpful in the treatment of ischemic stroke.

In an interventional trial involving 404 stroke patients, the aspirin and dipyridamole ER combination resulted in increased IGF-1 and decreased levels of IGFBP-3 (Armbrust et al., 2017). IGF-1 has been shown in animal studies to improve neurological dysfunction, cerebral infarction, brain edema and cognitive deficits (Yang et al., 2020; Bake et al., 2014). Preclinically, human recombinant IGF-1 alleviated the various neuropathological and behavioral conditions associated with stroke. Some of the critical findings of different animal studies on stroke include a reduction in infarct volume, iNOS, and decreased infiltration of polymorphonuclear leukocytes, as well as an increase in sensorimotor functions (Serhan et al., 2020; Bake et al., 2019; Okoreeh et al., 2017; Lin et al., 2011).

In a randomized controlled trial, exenatide at 5 μg and 10 μg doses were reported to aggravate stroke pathology while lowering plasma glucose levels (Muller et al., 2018; Larsson et al., 2019). The neuroprotective role of GLP-1 analogues in various neurodegenerative diseases has been well established in preclinical studies. Furthermore, GLP-1 receptor activators such as GLP-1(9−36) and exendin-4 have reduced infarct volume, astrogliosis, neuronal apoptosis, and neuroinflammation in stroke patients (Nizari et al., 2021; Huang et al., 2020). In a stroke model, 6,7-dichloro-2-methylsulfonyl-3-N-tert-butylaminoquinoxaline (DMB) increased cAMP levels while decreasing necrosis, apoptotic cell death, and cerebral infarct size (Zhang et al., 2016). IGF-1 and GLP-1 activators show promising therapeutic potential against neuronal damage during or after an ischaemic insult.

4.7. Traumatic brain injury (TBI)

TBI is a defined clinical condition that causes brain damage due to an external, sudden, and extreme force (Blennow et al., 2016). TBI manifests attention, memory, affectivity, behaviour, planning, and executive dysfunctions, significantly impacting the patient's and their family's quality of life (Constantinidou et al., 2012). Diffuse axonal injury, involving damage to cerebral white matter tracts, occurs in nearly all severities of TBI, acutely disrupting biochemical and cytoskeletal functions to produce physical, emotional, or cognitive symptoms (LoBue et al., 2019). Symptoms such as dizziness, headaches, problems with concentration and memory, blurred or double vision, nausea, sensitivity to light or noise, fatigue, restlessness, irritability, insomnia, depression and anxiety typically occur within the first few days after TBI (Polinder et al., 2018). IGF-1 and GLP-1 receptor activators have promising neuroprotective agents in TBI conditions.

IGF-1 was studied in a Phase IIa, randomized, double-blind, placebo-controlled trial involving 40 patients, and the results show a significant increase in IGF-1 levels in TBI (Dubiel et al., 2018). Furthermore, IGF-1 levels increased in TBI patients with growth hormones (Hatton et al., 2006). Carlsson and Saatman claimed that recombinant human IGF-1 increased hippocampal neurogenesis in vivo and reported an increase in IGF-1 levels in mice brains that promotes neurobehavioral recovery after TBI (Carlson and Saatman, 2018). Human IGF-1 vector cDNA (RAd-IGF1) reduces reactive microglia in the cerebral cortex of Wistar rats (Herrera et al., 2021). In both in-vivo and in-vitro studies, recombinant annexin A2 promotes cerebral angiogenesis and increases growth factors such as VEGF, ang1, Tie2 mRNA, eNOS, IGF-1, and BDNF (Cheng et al., 2021). Human IGF-1 and biotinylated human IGF-1 efficiently increased brain IGF-1 levels following traumatic brain injury (Santi et al., 2018).

GLP-1 receptor activators improved recovery after traumatic brain injury in rodent models. Exendin-4, for example, has demonstrated a promising neuroprotective role in various in-vivo studies by preventing cognitive, memory, and behavioral deficits as well as reducing cellular apoptosis and neuroinflammation, resulting in the eradication of neurological dysfunctions (Zhang et al., 2020; Rachmany et al., 2017; Tweedie et al., 2016). In TBI patients, liraglutide alone or combined with Twincertin reduces cerebral edema and neurodegeneration and improves cognitive and memory functions (Bader et al., 2020; Hakon et al., 2015; Li et al., 2015). In addition, sitagliptin has increased manganese superoxide dismutase and cAMP levels while decreasing lesion size in a TBI animal model (DellaValle et al., 2016). Clostridium butyricum has been shown to possess a neuroprotective effect by reducing neurological dysfunctions and brain edema. In an in-vivo model of TBI, increased intestinal GLP-1 secretion and cerebral GLP-1R expression were both observed (Li et al., 2018). Other GLP-1 activators, such as PT302, triagonist, and Human GIP, were investigated and found to have beneficial neuroprotective effects in TBI animal models (Bader et al., 2019; Y. Li et al., 2020; Yu et al., 2016). Furthermore, GLP-1 agonists have not been clinically investigated in TBI patients. As a result, clinical data are urgently needed to confirm the potential neuroprotective effects of GLP-1 receptor activators in humans. Furthermore, IGF-1 and GLP-1 receptor agonists have shown neuroprotective efficacy in TBI animal models and patients. The activation of IGF-1 and GLP-1 eventually results in a reduction in TBI-related neurocomplications, which could provide a foundation for future research in various neurodegenerative and neuropsychiatric disorders.

4.8. Depression

Depression, frequently referred to as major depressive disorder, is a severe neuropsychiatric disorder with a significant social impact and a high risk of becoming chronic (Perini et al., 2019). In depression, neuropathological conditions include serotonin deficiency, hypothalamic–pituitary–adrenal (HPA) axis dysregulation, and disruption of the continuous production of adult-generated neurons in the hippocampus's dentate gyrus (Troubat et al., 2021). Disruptions of cerebellarcerebral functional connectivity (FC) have been proposed as one of the neurobiological changes associated with depression and as one possible explanation for the cognitive and emotional deficits associated with this disease (Zhu et al., 2020). Depressed mood, anhedonia, decreased food intake, sleep disturbances, hyperactivity of the HPA axis, glucocorticoid resistance, loss of interest, and reduced energy are the primary symptoms of depression (Gold, 2015). It has been established through research findings that dysregulation of IGF-1 and GLP-1 causes depressive symptoms and that their analogues can alleviate complications by improving neuropathological conditions in depression.

PEG-IGF-1 has been tested in vivo, and the results indicate that it reduces inflammation, oxidative stress, and mitochondrial dysfunction associated with depression (Yang et al., 2021). IGF-1 has been studied in depression both in vivo and in vitro, demonstrating its neuroprotective role by increasing neuroplasticity and endogenous antioxidants, as well as a remarkable decrease in insulin/IGF-1 sensitivity (Mueller et al., 2018; Grinberg et al., 2017; Grinberg et al., 2012).

Preclinical studies on GLP-1 activators indicate they are critical in lessening neuropathological changes in depressive rat brains. For example, lixisenatide alleviates depressive and anxiety symptoms by promoting neurogenesis (Ren et al., 2021). Another beneficial GLP-1 analogue, Liraglutide, promotes improvement in pathological deficits such as increased phosphorylated GSK3β and mitigates stress hormone-induced hyperactivity (Weina et al., 2018). Additionally, preclinical administration of Exendin-4 for five days has reduced depressive-like symptoms (Ventorp et al., 2017). All the studies mentioned above indicate the potential contribution and central effects of IGF-1 and GLP-1 activators in improving depression.

4.9. Amyotrophic lateral sclerosis

ALS is a motor neuron disorder characterized by demyelination and oligodendrocyte destruction in the brain (Shandilya et al., 2021). It is accompanied by upper and lower motor dysfunctions that cause progressive weakness (Masrori and Damme, 2020). As ALS is a rare disorder, it remains undiagnosed and misunderstood (Ham et al., 2017). Besides the availability of various FDA-approved drugs, there is a lack of specific treatment options for ALS patients (Brown and Wobst, 2021). Ongoing research and current data on ALS suggest that there is a need for specific diagnostic biomarkers and therapeutic interventions to control the progression of ALS.

The downregulation of IGF-1 and GLP-1 signaling has been shown to be involved in the cytopathology of ALS. In ALS patients, intrathecal IGF-1 administration provides an effective treatment option for ALS by slowing down motor dysfunctions (Nagano et al., 2005). Moreover, further studies on a large patient population are needed to confirm its benefits and optimize dosages of IGF-1. Preclinically, IGF-1 has been investigated for its neuroprotective potential in ALS animal models. For instance, AAV-IGF-1 vector delivery in deep cerebellar nuclei of mice resulted in improved motor function and increased expression of the IGF-1 gene (Dodge et al., 2008). Additionally, 4-hydroxyisoleucine has recently been demonstrated to protect methylmercury-induced ALS rats by activating IGF-1 and GLP-1 signaling (Shandilya et al., 2022).

The findings of the in-vitro study indicate that exendin-4, a GLP-1 agonist, demonstrated its neuroprotective actions by decreasing oxidative stress and neuronal apoptosis (Li et al., 2012). The above evidence point toward the neuroprotective effects. At last, further studies on animals and large patient populations are needed to confirm the benefits and optimize dosages of IGF-1 and GLP-1 receptor activators in ALS disease.

5. Future perspectives

Although activation of IGF-1 and GLP-1 analogues are useful in treating diabetes mellitus, they are also demonstrated to be effective in neurological disorders. Many studies have indicated that IGF-1 and GLP-1 activators can be used as specific therapeutic agents in various neurodegenerative and neuropsychiatric disorders. Still, the neuroprotective efficacy of IGF-1 and GLP-1 receptor activators should be evaluated in other diseases like bipolar and multiple sclerosis. Moreover, protein biomolecules such as PI3/Akt kinase, mTOR, and MAPK/ERK are involved in both IGF-1 and GLP-1 signaling cascades. According to the evidence, IGF-1 and GLP-1 mimetics can treat a wide range of brain diseases. However, the mechanism by which they regulate each other's receptors is not clearly understood and is regarded as a matter of further research. Few studies show a link between GLP-1 analogues and IGF-1 receptor upregulation in ischemia and stroke (Zhang et al., 2021; Huang et al., 2020). Nevertheless, a better understanding of how they stimulate each other is considered necessary to maximise the neuroprotective benefits of IGF-1 and GLP-1 activators in other neurological disorders. Furthermore, future research must establish the relationship between IGF-1 and GLP-1 signalling and their activators in the brain.

6. Conclusion

IGF-1 and GLP-1 are two recently investigated cellular and molecular signaling targets that have been demonstrated to have beneficial effects on the CNS upon their upregulation. IGF-1 and GLP-1 stimulate neuronal development, proliferation, differentiation, and cell survival in the brain. Additionally, current research provides robust evidence regarding the neuroprotective potential of IGF-1 and/or GLP-1 receptor activators in preventing various neurodegenerative diseases. Moreover, preclinical and clinical studies demonstrate that IGF-1 and GLP-1 analogues augment cellular levels of IGF-1 and GLP-1, alleviating neurocomplications associated with various neurodegenerative disorders. The outcomes of these investigations indicate a decrease in neurological abnormalities related to the progression of neurodegenerative pathologies. Lastly, it can be stated that activators of the IGF-1 and GLP-1 receptors may be viable therapeutic agents for central nervous system complications.

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Not applicable.

References

Abbas, T., Faivre, E., Hölscher, C., 2009. Impairment of synaptic plasticity and memory formation in GLP-1 receptor KO mice: interaction between type 2 diabetes and Alzheimer's disease. Behav. Brain Res. 205 (1), 265–271.

Adams, T.E., Epa, V.C., Garrett, T.P.J., 2000. Structure and function of the type 1 insulin-like growth factor receptor. Cell. Mol. Life Sci. CMLS 57 (7), 1050–1093.

Ahad, M.A., Kumaran, K.R., Ning, T., Mansor, N.I., Effendy, M.A., Damodaran, T., Hassan, Z., 2020. Insights into the neuropathology of cerebral ischemia and its mechanisms. Rev. Neurosci. 31 (5), 521–538.

Aisen, P.S., Cummings, J., Jack, C.R., Morris, J.C., Sperling, R., Frölich, L., Dubois, B., 2017. On the path to 2025: understanding the Alzheimer's disease continuum. Alzheimer's Res. Ther. 9 (1), 1–10.

Altar, C.A., Hunt, R.A., Jurata, L.W., Webster, M.J., Derby, E., Gallagher, P., Lemire, A., Brockman, J., Laeng, P., 2008. Insulin, IGF-1, and muscarinic agonists modulate schizophrenia-associated genes in human neuroblastoma cells. Biol. Psychiatry 64 (12), 1077–1087. https://doi.org/10.1016/j.biopsych.2008.08.031.

Alvarez, E., Martínez, M.D., Roncero, I., Chowen, J.A., García-Cuartero, B., Gispert, J.D., Blázquez, E., 2005. The expression of GLP-1 receptor mRNA and protein allows the effect of GLP-1 on glucose metabolism in the human hypothalamus and brainstem. J. Neurochem. 92 (4), 798–806.

Ando, T., Hatada, K., Sata, M., Tachiki, H., Fukazawa, T., Kusumoto, S., Horie, I., Abiru, N., Matsumoto, S., Kawakami, A., 2018. Glucagon-like peptide-1 receptor

agonists as an effective therapeutic agent for diabetes mellitus and obesity in patients with schizophrenia under treatment with second-generation antipsychotics. Acta Med. Nagasaki. 61 (4), 151–157.
Armbrust, M., Worthmann, H., Dengler, R., Schumacher, H., Lichtinghagen, R., Eschenfelder, C.C., Endres, M., Ebinger, M., 2017. Circulating insulin-like growth factor-1 and insulin-like growth factor binding protein-3 predict three-months outcome after ischemic stroke. Exp. Clin. Endocrinol. Diabetes 125 (7), 485–491. https://doi.org/10.1055/s-0043-103965.
Athauda, D., Maclagan, K., Skene, S.S., Bajwa-Joseph, M., Letchford, D., Chowdhury, K., Hibbert, S., Budnik, N., Zampedri, L., Dickson, J., Li, Y., Aviles-Olmos, I., Warner, T. T., Limousin, P., Lees, A.J., Greig, N.H., Tebbs, S., Foltynie, T., 2017. Exenatide once weekly versus placebo in Parkinson's disease: a randomised, double-blind, placebo-controlled trial. Lancet 390 (10103), 1664–1675. https://doi.org/10.1016/S0140-6736(17)31585-4.
Aviles-Olmos, I., Dickson, J., Kefalopoulou, Z., Djamshidian, A., Ell, P., Soderlund, T., Whitton, P., Wyse, R., Isaacs, T., Lees, A., Limousin, P., Foltynie, T., 2013. Exenatide and the treatment of patients with Parkinson's disease. J. Clin. Investig. 123 (6), 2730–2736. https://doi.org/10.1172/JCI68295.
Aviles-Olmos, I., Dickson, J., Kefalopoulou, Z., Djamshidian, A., Kahan, J., Ell, P., Whitton, P., Wyse, R., Isaacs, T., Lees, A., Limousin, P., Foltynie, T., 2015. Motor and cognitive advantages persist 12 months after exenatide exposure in Parkinson's disease. J. Parkinson's Dis. 4 (3), 337–344. https://doi.org/10.3233/JPD-140364.
Bader, M., Li, Y., Lecca, D., Rubovitch, V., Tweedie, D., Glotfelty, E., Rachmany, L., Kim, H.K., Choi, H., Il, Hoffer, B.J., Pick, C.G., Greig, N.H., Kim, D.S., 2019. Pharmacokinetics and efficacy of PT302, a sustained-release Exenatide formulation, in a murine model of mild traumatic brain injury. Neurobiol. Dis. 124, 439–453. https://doi.org/10.1016/j.nbd.2018.11.023.
Bader, M., Li, Y., Tweedie, D., Shlobin, N.A., Bernstein, A., Rubovitch, V., Tovar-y-Romo, L.B., DiMarchi, R.D., Hoffer, B.J., Greig, N.H., Pick, C.G., 2020. Neuroprotective effects and treatment potential of incretin mimetics in a murine model of mild traumatic brain injury. Front. Cell Dev. Biol. 7 (January), 1–18. https://doi.org/10.3389/fcell.2019.00356.
Baggio, L.L., Drucker, D.J., 2007. Biology of incretins: GLP-1 and GIP. Gastroenterology 132 (6), 2131–2157.
Bake, S., Selvamani, A., Cherry, J., Sohrabji, F., 2014. Blood brain barrier and neuroinflammation are critical targets of IGF-1-mediated neuroprotection in stroke for middle-aged female rats. PLoS One 9 (3). https://doi.org/10.1371/journal.pone.0091427.
Bake, S., Okoreeh, A., Khosravian, H., Sohrabji, F., 2019. Insulin-like Growth Factor (IGF)-1 treatment stabilizes the microvascular cytoskeleton under ischemic conditions. Exp. Neurol. 311 (July 2018), 162–172. https://doi.org/10.1016/j.expneurol.2018.09.016.
Baker, L.D., Barsness, S.M., Borson, S., Merriam, G.R., Friedman, S.D., Craft, S., Vitiello, M.V., 2012. Effects of growth hormone-releasing hormone on cognitive function in adults with mild cognitive impairment and healthy older adults: results of a controlled trial. Arch. Neurol. 69 (11), 1420–1429. https://doi.org/10.1001/archneurol.2012.1970.
Barnat, M., Capizzi, M., Aparicio, E., Boluda, S., Wennagel, D., Kacher, R., Humbert, S., 2020. Huntington's disease alters human neurodevelopment. Science 369 (6505), 787–793.
Beck, K.D., Powell-Braxton, L., Widmer, H.R., Valverde, J., Hefti, F., 1995. Igf1 gene disruption results in reduced brain size, CNS hypomyelination, and loss of hippocampal granule and striatal parvalbumin-containing neurons. Neuron 14 (4), 717–730.
Blennow, K., Brody, D.L., Kochanek, P.M., Levin, H., McKee, A., Ribbers, G.M., Zetterberg, H., 2016. Traumatic brain injuries. Nat. Rev. Dis. Prim. 2 (1), 1–19.
Bomfim, T.R., Forny-Germano, L., Sathler, L.B., Brito-Moreira, J., Houzel, J.C., Decker, H., Silverman, M.A., Kazi, H., Melo, H.M., McClean, P.L., Holscher, C., Arnold, S.E., Talbot, K., Klein, W.L., Munoz, D.P., Ferreira, S.T., De Felice, F.G., 2012. An anti-diabetes agent protects the mouse brain from defective insulin signaling caused by Alzheimer's disease-associated Aβ oligomers. J. Clin. Investig. 122 (4), 1339–1353. https://doi.org/10.1172/JCI57256.
Bozdagi, O., Tavassoli, T., Buxbaum, J.D., 2013. Insulin-like growth factor-1 rescues synaptic and motor deficits in a mouse model of autism and developmental delay. Mol. Autism 4 (1), 1–4.
Briggs, R., Kennelly, S.P., O'Neill, D., 2016. Drug treatments in Alzheimer's disease. Clin. Med. 16 (3), 247.
Britsch, S., Krippeitdrews, P., Lang, F., Gregor, M., Drews, G., 1995. Glucagon-like peptide-1 modulates Ca2+ current but not K+ ATP current in intact mouse pancreatic B-cells. Biochem. Biophys. Res. Commun. 207 (1), 33–39.
Brown, D.G., Wobst, H.J., 2021. A decade of FDA-approved drugs (2010–2019): trends and future directions. J. Med. Chem. 64 (5), 2312–2338.
Bryan, M.R., Nordham, K.D., Rose, D.I.R., O'Brien, M.T., Joshi, P., Foshage, A.M., Gonçalves, F.M., Nitin, R., Uhouse, M.A., Aschner, M., Bowman, A.B., 2020. Manganese acts upon insulin/igf receptors to phosphorylate AKT and increase glucose uptake in Huntington's disease cells. Mol. Neurobiol. 57 (3), 1570–1593. https://doi.org/10.1007/s12035-019-01824-1.
Cahlin, F. (2021). The Association Between Whole Blood Viscosity and Cerebral Infarct Growth in Acute Ischemic Stroke: A Pilot Study.
Cai, H.Y., Yang, J.T., Wang, Z.J., Zhang, J., Yang, W., Wu, M.N., Qi, J.S., 2018. Lixisenatide reduces amyloid plaques, neurofibrillary tangles and neuroinflammation in an APP/PS1/tau mouse model of Alzheimer's disease. Biochem. Biophys. Res. Commun. 495 (1), 1034–1040. https://doi.org/10.1016/j.bbrc.2017.11.114.
Calsolaro, V., Edison, P., 2016. Neuroinflammation in Alzheimer's disease: current evidence and future directions. Alzheimer's Dement. 12 (6), 719–732.
Cao, Y., Hölscher, C., Hu, M.M., Wang, T., Zhao, F., Bai, Y., Zhang, J., Wu, M.N., Qi, J.S., 2018. DA5-CH, a novel GLP-1/GIP dual agonist, effectively ameliorates the cognitive impairments and pathology in the APP/PS1 mouse model of Alzheimer's disease. Eur. J. Pharmacol. 827, 215–226. https://doi.org/10.1016/j.ejphar.2018.03.024.
Carlson, S.W., Saatman, K.E., 2018. Central infusion of insulin-like growth factor-1 increases hippocampal neurogenesis and improves neurobehavioral function after traumatic brain injury. J. Neurotrauma 35 (13), 1467–1480. https://doi.org/10.1089/neu.2017.5374.
Carroll, J.B., Bates, G.P., Steffan, J., Saft, C., Tabrizi, S.J., 2015. Treating the whole body in Huntington's disease. Lancet Neurol. 14 (11), 1135–1142.
Cerveri, G., Gesi, C., Mencacci, C., 2019. Pharmacological treatment of negative symptoms in schizophrenia: update and proposal of a clinical algorithm. Neuropsychiatr. Dis. Treat.
Chaker, Z., George, C., Petrovska, M., Caron, J.B., Lacube, P., Caillé, I., Holzenberger, M., 2016. Hypothalamic neurogenesis persists in the aging brain and is controlled by energy-sensing IGF-I pathway. Neurobiol. Aging 41, 64–72.
Chang, C.C., Lin, T.C., Ho, H.L., Kuo, C.Y., Li, H.H., Korolenko, T.A., Chen, W.J., Lai, T.J., Ho, Y.J., Lin, C.L., 2018. GLP-1 analogue liraglutide attenuates mutant huntingtin-induced neurotoxicity by restoration of neuronal insulin signaling. Int. J. Mol. Sci. 19 (9) https://doi.org/10.3390/ijms19092505.
Chen, S., Sun, J., Zhao, G., Guo, A., Chen, Y., Fu, R., Deng, Y., 2017. Liraglutide improves water maze learning and memory performance while reduces hyperphosphorylation of tau and neurofilaments in APP/PS1/Tau triple transgenic mice. Neurochem. Res. 42 (8), 2326–2335. https://doi.org/10.1007/s11064-017-2250-8.
Chen, S., Zhou, M., Sun, J., Guo, A., Fernando, R.L., Chen, Y., Deng, Y., 2019. DPP-4 inhibitor improves learning and memory deficits and AD-like neurodegeneration by modulating the GLP-1 signaling. Neuropharmacology 157, 107668.
Cheng, B., Anand, P., Kuang, A., Akhtar, F., Scofield, V.L., 2016. N-Acetylcysteine in combination with IGF-1 enhances neuroprotection against proteasome dysfunction-induced neurotoxicity in SH-SY5Y cells. Parkinson's Dis. *2016*. https://doi.org/10.1155/2016/6564212.
Cheng, C., Wang, X., Jiang, Y., Li, Y., Liao, Z., Li, W., Wang, X., 2021. Recombinant annexin A2 administration improves neurological outcomes after traumatic brain injury in mice. Front. Pharmacol. 12.
Cheng, C.M., Reinhardt, R.R., Lee, W.H., Joncas, G., Patel, S.C., Bondy, C.A., 2000. Insulin-like growth factor 1 regulates developing brain glucose metabolism. Proc. Natl. Acad. Sci. 97 (18), 10236–10241.
Cho, Y.M., Fujita, Y., Kieffer, T.J., 2014. Glucagon-like peptide-1: glucose homeostasis and beyond. Annu. Rev. Physiol. 76, 535–559.
Chung, D.W., Fish, K.N., Lewis, D.A., 2016. Pathological basis for deficient excitatory drive to cortical parvalbumin interneurons in schizophrenia. Am. J. Psychiatry 173 (11), 1131–1139.
Constantinidou, F., Wertheimer, J.C., Tsanadis, J., Evans, C., Paul, D.R., 2012. Assessment of executive functioning in brain injury: collaboration between speech-language pathology and neuropsychology for an integrative neuropsychological perspective. Brain Inj. 26 (13–14), 1549–1563.
Cordeiro, L.M., Machado, M.L., da Silva, A.F., Obetine Baptista, F.B., da Silveira, T.L., Soares, F.A.A., Arantes, L.P., 2020. Rutin protects Huntington's disease through the insulin/IGF1 (IIS) signaling pathway and autophagy activity: study in Caenorhabditis elegans model. Food Chem. Toxicol. 141(March) https://doi.org/10.1016/j.fct.2020.111323.
Cork, S.C., Richards, J.E., Holt, M.K., Gribble, F.M., Reimann, F., Trapp, S., 2015. Distribution and characterisation of Glucagon-like peptide-1 receptor expressing cells in the mouse brain. Mol. Metab. 4 (10), 718–731.
Czech, M.P., 1989. Signal transmission by the insulin-like growth factors. Cell 59 (2), 235–238.
Czekus, C., Steullet, P., Rusterholz, T., Bozic, I., Do Cuenod, K., Bandarabadi, M., & Herrera, C.G. (2021). Deficient thalamo-cortical networks dynamics and sleep homeostatic processes in a redox dysregulation model relevant to schizophrenia. bioRxiv.
Dai, Z., Stiles, A.D., Moats-Staats, B., Van Wyk, J.J., D'Ercole, A.J., 1992. Interaction of secreted insulin-like growth factor-I (IGF-I) with cell surface receptors is the dominant mechanism of IGF-I's autocrine actions. J. Biol. Chem. 267 (27), 19565–19571.
De Graaf, C., Donnelly, D., Wootten, D., Lau, J., Sexton, P.M., Miller, L.J., Wang, M.W., 2016. Glucagon-like peptide-1 and its class BG protein–coupled receptors: a long march to therapeutic successes. Pharmacol. Rev. 68 (4), 954–1013.
Delafontaine, P., Song, Y.H., Li, Y., 2004. Expression, regulation, and function of IGF-1, IGF-1R, and IGF-1 binding proteins in blood vessels. Arterioscler., Thromb., Vasc. Biol. 24 (3), 435–444.
DellaValle, B., Hempel, C., Johansen, F.F., Kurtzhals, J.A.L., 2014. GLP-1 improves neuropathology after murine cold lesion brain trauma. Ann. Clin. Transl. Neurol. 1 (9), 721–732. https://doi.org/10.1002/acn3.99.
DellaValle, B., Brix, G.S., Brock, B., Gejl, M., Rungby, J., Larsen, A., 2016. Oral administration of sitagliptin activates creb and is neuroprotective in murine model of brain trauma. Front. Pharmacol. 7 (DEC), 1–8. https://doi.org/10.3389/fphar.2016.00450.
Dickson, D.W., 2018. Neuropathology of Parkinson disease. Park. Relat. Disord. 46, S30–S33.
Dik, M.G., Pluijm, S.M., Jonker, C., Deeg, D.J., Lomecky, M.Z., Lips, P., 2003. Insulin-like growth factor I (IGF-I) and cognitive decline in older persons. Neurobiol. Aging 24 (4), 573–581.
Dixit, T.S., Sharma, A.N., Lucot, J.B., Elased, K.M., 2013. Antipsychotic-like effect of GLP-1 agonist liraglutide but not DPP-IV inhibitor sitagliptin in mouse model for psychosis. Physiol. Behav. 114–115, 38–41. https://doi.org/10.1016/j.physbeh.2013.03.008.

Dodge, J.C., Haidet, A.M., Yang, W., Passini, M.A., Hester, M., Clarke, J., Kaspar, B.K., 2008. Delivery of AAV-IGF-1 to the CNS extends survival in ALS mice through modification of aberrant glial cell activity. Mol. Ther. 16 (6), 1056–1064.
Drucker, D.J., Philippe, J., Mojsov, S., Chick, W.L., Habener, J.F., 1987. Glucagon-like peptide I stimulates insulin gene expression and increases cyclic AMP levels in a rat islet cell line. Proc. Natl. Acad. Sci. 84 (10), 3434–3438.
Duarte, A.I., Petit, G.H., Ranganathan, S., Li, J.Y., Oliveira, C.R., Brundin, P., Björkqvist, M., Rego, A.C., 2011. IGF-1 protects against diabetic features in an in vivo model of Huntington's disease. Exp. Neurol. 231 (2), 314–319. https://doi.org/10.1016/j.expneurol.2011.06.016.
Duarte, Ana I., Sjögren, M., Santos, M.S., Oliveira, C.R., Moreira, P.I., Björkqvist, M., 2018. Dual therapy with liraglutide and ghrelin promotes brain and peripheral energy metabolism in the R6/2 mouse model of Huntington's disease. Sci. Rep. 8 (1), 1–14. https://doi.org/10.1038/s41598-018-27121-w.
Dubiel, R., Callender, L., Dunklin, C., Harper, C., Bennett, M., Kreber, L., Auchus, R., Diaz-Arrastia, R., 2018. Phase 2 randomized, placebo-controlled clinical trial of recombinant human growth hormone (rhGH) during rehabilitation from traumatic brain injury. Front. Endocrinol. 9 (SEP), 1–11. https://doi.org/10.3389/fendo.2018.00520.
Dubois, B., Villain, N., Frisoni, G.B., Rabinovici, G.D., Sabbagh, M., Cappa, S., Feldman, H.H., 2021. Clinical diagnosis of Alzheimer's disease: recommendations of the International Working Group. Lancet Neurol. 20 (6), 484–496.
Duda, P., Wiśniewski, J., Wójtowicz, T., Wójcicka, O., Jaśkiewicz, M., Drulis-Fajdasz, D., Gizak, A., 2018. Targeting GSK3 signaling as a potential therapy of neurodegenerative diseases and aging. Expert Opin. Ther. Targets 22 (10), 833–848.
During, M.J., Cao, L., Zuzga, D.S., Francis, J.S., Fitzsimons, H.L., Jiao, X., Haile, C.N., 2003. Glucagon-like peptide-1 receptor is involved in learning and neuroprotection. Nat. Med. 9 (9), 1173–1179.
Eakin, K., Li, Y., Chiang, Y.H., Hoffer, B.J., Rosenheim, H., Greig, N.H., Miller, J.P., 2013. Exendin-4 ameliorates traumatic brain injury-induced cognitive impairment in rats. PLoS ONE 8 (12), 1–8. https://doi.org/10.1371/journal.pone.0082016.
Evers, K., Maljaars, J., Carrington, S.J., Carter, A.S., Happé, F., Steyaert, J., Noens, I., 2021. How well are DSM-5 diagnostic criteria for ASD represented in standardized diagnostic instruments? Eur. Child Adolesc. Psychiatry 30 (1), 75–87.
Fadl, N.N., Ahmed, H.H., Booles, H.F., Sayed, A.H., 2013. Serrapeptase and nattokinase intervention for relieving Alzheimer's disease pathophysiology in rat model. Hum. Exp. Toxicol. 32 (7), 721–735. https://doi.org/10.1177/0960327112467040.
Fan, D., Alamri, Y., Liu, K., Macaskill, M., Harris, P., Brimble, M., Dalrymple-Alford, J., Prickett, T., Menzies, O., Laurenson, A., Anderson, T., Guan, J., 2018. Supplementation of blackcurrant anthocyanins increased cyclic glycine-proline in the cerebrospinal fluid of parkinson patients: Potential treatment to improve insulin-like growth factor-1 function. Nutrients 10 (6). https://doi.org/10.3390/nu10060714.
Farias Quipildor, G.E., Mao, K., Hu, Z., Novaj, A., Cui, M.H., Gulinello, M., Huffman, D. M., 2019. Central IGF-1 protects against features of cognitive and sensorimotor decline with aging in male mice. Geroscience 41 (2), 185–208.
Femminella, G.D., Frangou, E., Love, S.B., Busza, G., Holmes, C., Ritchie, C., Edison, P., 2019. Evaluating the effects of the novel GLP-1 analogue liraglutide in Alzheimer's disease: study protocol for a randomised controlled trial (ELAD study). Trials 20 (1), 1–10.
Feng, P., Zhang, X., Li, D., Ji, C., Yuan, Z., Wang, R., Xue, G., Li, G., Hölscher, C., 2018. Two novel dual GLP-1/GIP receptor agonists are neuroprotective in the MPTP mouse model of Parkinson's disease. Neuropharmacology 133, 385–394. https://doi.org/10.1016/j.neuropharm.2018.02.012.
Ferreira-Vieira, H., M, T., Guimaraes, I., Silva, F, R., M Ribeiro, F., 2016. Alzheimer's disease: targeting the cholinergic system. Curr. Neuropharmacol. 14 (1), 101–115.
Fombonne, E., Rogé, B., Claverie, J., Courty, S., Fremolle, J., 1999. Microcephaly and macrocephaly in autism. J. Autism Dev. Disord. 29 (2), 113–119.
Foti, M., Ahmed Moukil, M., Dudognon, P., Carpentier, J.L., 2004. Insulin and IGF-1 receptor trafficking and signalling (September). In: Biology of IGF-1: Its Interaction with Insulin in Health and Malignant States: Novartis Foundation Symposium, vol. 262. Chichester, UK: John Wiley & Sons, Ltd, pp. 125–147 (September).
Friedman, S.D., Baker, L.D., Borson, S., Jensen, J.E., Barsness, S.M., Craft, S., Merriam, G. R., Otto, R.K., Novotny, E.J., Vitiello, M.V., 2013. Growth hormone-releasing hormone effects on brain γ-aminobutyric acid levels in mild cognitive impairment and healthy aging. JAMA Neurol. 70 (7), 883–890. https://doi.org/10.1001/jamaneurol.2013.1425.
Fuentes-Santamaría, V., Alvarado, J.C., Rodriguez-De La Rosa, L., Murillo-Cuesta, S., Contreras, J., Juiz, J.M., Varela-Nieto, I., 2016. IGF-1 deficiency causes atrophic changes associated with upregulation of VGluT1 and downregulation of MEF2 transcription factors in the mouse cochlear nuclei. Brain Struct. Funct. 221 (2), 709–734.
Gabbouj, S., Ryhänen, S., Marttinen, M., Wittrahm, R., Takalo, M., Kemppainen, S., Natunen, T., 2019. Altered insulin signaling in Alzheimer's disease brain–special emphasis on PI3K-Akt pathway. Front. Neurosci. 13, 629.
Gao, C., Liu, Y., Jiang, Y., Ding, J., Li, L., 2014. Geniposide ameliorates learning memory deficits, reduces tau phosphorylation and decreases apoptosis via GSK3β Pathway in streptozotocin-induced Alzheimer rat model. Brain Pathol. 24 (3), 261–269. https://doi.org/10.1111/bpa.12116.
Gao, Q.G., Chen, W.F., Xie, J.X., Wong, M.S., 2009. Ginsenoside Rg1 protects against 6-OHDA-induced neurotoxicity in neuroblastoma SK-N-SH cells via IGF-I receptor and estrogen receptor pathways. J. Neurochem. 109 (5), 1338–1347. https://doi.org/10.1111/j.1471-4159.2009.06051.x.
Gejl, M., Gjedde, A., Egefjord, L., Møller, A., Hansen, S.B., Vang, K., Rodell, A., Brændgaard, H., Gottrup, H., Schacht, A., Møller, N., Brock, B., Rungby, J., 2016. In Alzheimer's disease, 6-month treatment with GLP-1 analog prevents decline of brain glucose metabolism: Randomized, placebo-controlled, double-blind clinical trial. Front. Aging Neurosci. 8 (May), 1–10. https://doi.org/10.3389/fnagi.2016.00108.
Girnita, L., Worrall, C., Takahashi, S.I., Seregard, S., Girnita, A., 2014. Something old, something new and something borrowed: emerging paradigm of insulin-like growth factor type 1 receptor (IGF-1R) signaling regulation. Cell. Mol. life Sci. 71 (13), 2403–2427.
Glaze, D.G., Neul, J.L., Kaufmann, W.E., Berry-Kravis, E., Condon, S., Stoms, G., Oosterholt, S., Della Pasqua, O., Glass, L., Jones, N.E., Percy, A.K., 2019. Double-blind, randomized, placebo-controlled study of trofinetide in pediatric Rett syndrome. Neurology 92 (16), E1912–E1925. https://doi.org/10.1212/WNL.0000000000007316.
Gold, P.W., 2015. The organization of the stress system and its dysregulation in depressive illness. Mol. Psychiatry 20 (1), 32–47.
Grinberg, Y.Y., Van Drongelen, W., Kraig, R.P., 2012. Insulin-like growth factor-1 lowers spreading depression susceptibility and reduces oxidative stress. J. Neurochem. 122 (1), 221–229. https://doi.org/10.1111/j.1471-4159.2012.07763.x.
Grinberg, Y.Y., Zitzow, L.A., Kraig, R.P., 2017. Intranasally administered IGF-1 inhibits spreading depression in vivo. Brain Res. 1677 (September), 47–57. https://doi.org/10.1016/j.brainres.2017.09.022.
Hakon, J., Ruscher, K., Romner, B., Tomasevic, G., 2015. Preservation of the blood brain barrier and cortical neuronal tissue by Liraglutide, a long acting glucagon-like-1 analogue, after experimental traumatic brain injury. PLoS One 10 (3), 1–17. https://doi.org/10.1371/journal.pone.0120074.
Hall, C., Yu, H., Choi, E., 2020. Insulin receptor endocytosis in the pathophysiology of insulin resistance. Exp. Mol. Med. 52 (6), 911–920.
Ham, H., Lee, B.I., Oh, H.J., Park, S.H., Kim, J.S., Park, J.M., Choi, M.G., 2017. A case of celiac disease with neurologic manifestations misdiagnosed as amyotrophic lateral sclerosis. Intest. Res. 15 (4), 540.
Hamilton, A., Hölscher, C., 2009. Receptors for the incretin glucagon-like peptide-1 are expressed on neurons in the central nervous system. Neuroreport 20 (13), 1161–1166.
Hatton, J., Kryscio, R., Ryan, M., Linda, O., Young, B., 2006. Systemic metabolic effects of combined insulin-like growth factor-I and growth hormone therapy in patients who have sustained acute traumatic brain injury. J. Neurosurg. 105 (6), 843–852. https://doi.org/10.3171/jns.2006.105.6.843.
Hernández, C., Bogdanov, P., Corraliza, L., García-Ramírez, M., Solà-Adell, C., Arranz, J. A., Simó, R., 2016. Topical administration of GLP-1 receptor agonists prevents retinal neurodegeneration in experimental diabetes. Diabetes 65 (1), 172–187.
Herrera, M.L., Bandín, S., Champarini, L.G., Hereñú, C.B., Bellini, M.J., 2021. Intramuscular insulin-like growth factor-1 gene therapy modulates reactive microglia after traumatic brain injury. Brain Res. Bull. 175 (October 2020), 196–204. https://doi.org/10.1016/j.brainresbull.2021.07.023.
Hirsch, L., Jette, N., Frolkis, A., Steeves, T., Pringsheim, T., 2016. The incidence of Parkinson's disease: a systematic review and meta-analysis. Neuroepidemiology 46 (4), 292–300.
Holst, J.J., 2007. The physiology of glucagon-like peptide 1. Physiol. Rev. 87 (4), 1409–1439.
Holz, G.G., Leech, C.A., Habener, J.F., 1995. Activation of a cAMP-regulated Ca2+-signaling pathway in pancreatic β-Cells by the insulinotropic hormone glucagon-like peptide-1 (*). J. Biol. Chem. 270 (30), 17749–17757.
Hou, X., Jin, Y., Chen, J., Hong, Y., Luo, D., Yin, Q., Liu, X., 2017. IGF-1 protects against Aβ25-35-induced neuronal cell death via inhibition of PUMA expression and Bax activation. Neurosci. Lett. 637, 188–194. https://doi.org/10.1016/j.neulet.2016.11.012.
Hu, M., Li, F., Wang, W., 2018. Vitexin protects dopaminergic neurons in mptp-induced parkinson's disease through pi3k/akt signaling pathway. Drug Des., Dev. Ther. 12, 565–573. https://doi.org/10.2147/DDDT.S156920.
Huang, C., Yuan, L., Cao, S., 2015. Endogenous GLP-1 as a key self-defense molecule against lipotoxicity in pancreatic islets. Int. J. Mol. Med. 36 (1), 173–185.
Huang, J., Liu, Y., Cheng, L., Li, J., Zhang, T., Zhao, G., Zhang, H., 2020. Glucagon-like peptide-1 cleavage product GLP-1(9–36) reduces neuroinflammation from stroke via the activation of insulin-like growth factor 1 receptor in astrocytes. Eur. J. Pharmacol. 887, 173581 https://doi.org/10.1016/j.ejphar.2020.173581.
Hui, C., Tadi, P., Patti, L., 2018. Ischemic Stroke.
Insel, T.R., 2010. Rethinking schizophrenia. Nature 468 (7321), 187–193.
Ishøy, P.L., Knop, F.K., Broberg, B.V., Baandrup, L., Fagerlund, B., Jørgensen, N.R., Ebdrup, B.H., 2014. Treatment of antipsychotic-associated obesity with a GLP-1 receptor agonist—protocol for an investigator-initiated prospective, randomised, placebo-controlled, double-blinded intervention study: the TAO study protocol. BMJ Open 4 (1), e004158.
Ishøy, P.L., Knop, F.K., Broberg, B.V., Bak, N., Andersen, U.B., Jørgensen, N.R., Ebdrup, B.H., 2017. Effect of GLP-1 receptor agonist treatment on body weight in obese antipsychotic-treated patients with schizophrenia: a randomized, placebo-controlled trial. Diabetes, Obes. Metab. 19 (2), 162–171.
Iwai, T., Ito, S., Tanimitsu, K., Udagawa, S., Oka, J.I., 2006. Glucagon-like peptide-1 inhibits LPS-induced IL-1β production in cultured rat astrocytes. Neurosci. Res. 55 (4), 352–360.
Jacobs, S., Kull Jr, F.C., Earp, H.S., Svoboda, M.E., Van Wyk, J.J., Cuatrecasas, P., 1983. Somatomedin-C stimulates the phosphorylation of the beta-subunit of its own receptor. J. Biol. Chem. 258 (16), 9581–9584.
Jalewa, J., Sharma, M.K., Gengler, S., Hölscher, C., 2017. A novel GLP-1/GIP dual receptor agonist protects from 6-OHDA lesion in a rat model of Parkinson's disease. Neuropharmacology 117, 238–248. https://doi.org/10.1016/j.neuropharm.2017.02.013.
Janowska, J., Gargas, J., Ziemka-Nalecz, M., Zalewska, T., Sypecka, J., 2020. Oligodendrocyte response to pathophysiological conditions triggered by episode of

perinatal hypoxia-ischemia: role of IGF-1 secretion by glial cells. Mol. Neurobiol. 57 (10), 4250–4268.
Järvinen, A., Laine, M.K., Tikkanen, R., Castrén, M.L., 2019. Beneficial effects of GLP-1 agonist in a Male with compulsive food-related behavior associated with autism. Front. Psychiatry 10 (MAR), 10–14. https://doi.org/10.3389/fpsyt.2019.00097.
Jellinger, K.A., 2015. Neuropathobiology of non-motor symptoms in Parkinson disease. J. Neural Transm. 122 (10), 1429–1440.
Ji, C., Xue, G.F., Lijun, C., Feng, P., Li, D., Li, L., Li, G., Hölscher, C., 2016. A novel dual GLP-1 and GIP receptor agonist is neuroprotective in the MPTP mouse model of Parkinson′s disease by increasing expression of BNDF. Brain Res. 1634, 1–11. https://doi.org/10.1016/j.brainres.2015.09.035.
Jiang, J., Lv, X., Wu, X., Yang, Y., Jiang, H., 2017. Downregulation of circulating insulin-like growth factor 1 contributes to memory impairment in aged mice after sevoflurane anesthesia. Behav. Pharmacol. 28 (2), 238–243.
Kang, G., Chepurny, O.G., Malester, B., Rindler, M.J., Rehmann, H., Bos, J.L., Holz, G.G., 2006. cAMP sensor Epac as a determinant of ATP-sensitive potassium channel activity in human pancreatic β cells and rat INS-1 cells. J. Physiol. 573 (3), 595–609.
Kappeler, L., Filho, C.D.M., Dupont, J., Leneuve, P., Cervera, P., Périn, L., Holzenberger, M., 2008. Brain IGF-1 receptors control mammalian growth and lifespan through a neuroendocrine mechanism. PLoS Biol. 6 (10), e254.
Kastin, A.J., Akerstrom, V., Pan, W., 2002. Interactions of glucagon-like peptide-1 (GLP-1) with the blood-brain barrier. J. Mol. Neurosci. 18 (1), 7–14.
Khwaja, O.S., Ho, E., Barnes, K.V., O'Leary, H.M., Pereira, L.M., Finkelstein, Y., Kaufmann, W.E., 2014. Safety, pharmacokinetics, and preliminary assessment of efficacy of mecasermin (recombinant human IGF-1) for the treatment of Rett syndrome. Proc. Natl. Acad. Sci. 111 (12), 4596–4601.
Kleinridders, A., 2016. Deciphering brain insulin receptor and insulin-like growth factor 1 receptor signalling. J. Neuroendocrinol. 28, 11.
Koole, C., Pabreja, K., Savage, E.E., Wootten, D., Furness, S.G., Miller, L.J., Sexton, P.M., 2013. Recent advances in understanding GLP-1R (glucagon-like peptide-1 receptor) function. Biochem. Soc. Trans. 41 (1), 172–179.
Krishna, M., Narang, H., 2008. The complexity of mitogen-activated protein kinases (MAPKs) made simple. Cell. Mol. Life Sci. 65 (22), 3525–3544.
Kumar, A., Singh, A., 2015. A review on mitochondrial restorative mechanism of antioxidants in Alzheimer's disease and other neurological conditions. Front. Pharmacol. 6, 206.
Kwon, C.H., Luikart, B.W., Powell, C.M., Zhou, J., Matheny, S.A., Zhang, W., Parada, L.F., 2006. Pten regulates neuronal arborization and social interaction in mice. Neuron 50 (3), 377–388.
Lanctôt, K.L., Amatniek, J., Ancoli-Israel, S., Arnold, S.E., Ballard, C., Cohen-Mansfield, J., Boot, B., 2017. Neuropsychiatric signs and symptoms of Alzheimer's disease: New treatment paradigms. Alzheimer'S. Dement.: Transl. Res. Clin. Interv. 3 (3), 440–449.
Laron, Z., 2001. Insulin-like growth factor 1 (IGF-1): a growth hormone. Mol. Pathol. 54 (5), 311.
Larsson, M., Castrén, M., Lindström, V., von Euler, M., Patrone, C., Wahlgren, N., Nathanson, D., 2019. Prehospital exenatide in hyperglycemic stroke—A randomized trial. Acta Neurol. Scand. 140 (6), 443–448.
Lee, R.H., Lee, M.H., Wu, C.Y., e Silva, A.C., Possoit, H.E., Hsieh, T.H., Lin, H.W., 2018. Cerebral ischemia and neuroregeneration. Neural Regen. Res. 13 (3), 373.
Lewis, J., Dickson, D.W., 2016. Propagation of tau pathology: hypotheses, discoveries, and yet unresolved questions from experimental and human brain studies. Acta Neuropathol. 131 (1), 27–48.
Li, H., Sun, J., Du, J., Wang, F., Fang, R., Yu, C., Liu, J., 2018. Clostridium butyricum exerts a neuroprotective effect in a mouse model of traumatic brain injury via the gut-brain axis. Neurogastroenterol. Motil. 30 (5), e13260.
Li, T., Tu, L., Gu, R., Yang, X.L., Liu, X.J., Zhang, G.P., Tian, J.Y., 2020. Neuroprotection of GLP-1/GIP receptor agonist via inhibition of mitochondrial stress by AKT/JNK pathway in a Parkinson's disease model. Life Sci. 256, 117824.
Li, Y., Chigurupati, S., Holloway, H.W., Mughal, M., Tweedie, D., Bruestle, D.A., Greig, N.H., 2012. Exendin-4 ameliorates motor neuron degeneration in cellular and animal models of amyotrophic lateral sclerosis. PloS One 7 (2), e32008.
Li, Y., Bader, M., Tamargo, I., Rubovitch, V., Tweedie, D., Pick, C.G., Greig, N.H., 2015. Liraglutide is neurotrophic and neuroprotective in neuronal cultures and mitigates mild traumatic brain injury in mice. J. Neurochem. 135 (6), 1203–1217.
Li, Y., Glotfelty, E.J., Namdar, I., Tweedie, D., Olson, L., Hoffer, B.J., Greig, N.H., 2020. Neurotrophic and neuroprotective effects of a monomeric GLP-1/GIP/Gcg receptor triagonist in cellular and rodent models of mild traumatic brain injury. Exp. Neurol. 324, 113113.
Lin, S., Rhodes, P.G., Cai, Z., 2011. Whole body hypothermia broadens the therapeutic window of intranasally administered IGF-1 in a neonatal rat model of cerebral hypoxia–ischemia. Brain Res. 1385, 246–256.
Linker, S.B., Mendes, A.P., Marchetto, M.C., 2020. IGF-1 treatment causes unique transcriptional response in neurons from individuals with idiopathic autism. Mol. Autism 11 (1), 1–13.
Liu, J.P., Baker, J., Perkins, A.S., Robertson, E.J., Efstratiadis, A., 1993. Mice carrying null mutations of the genes encoding insulin-like growth factor I (Igf-1) and type 1 IGF receptor (Igf1r). Cell 75 (1), 59–72.
Liu, W., Jalewa, J., Sharma, M., Li, G., Li, L., Hölscher, C., 2015. Neuroprotective effects of lixisenatide and liraglutide in the 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine mouse model of Parkinson's disease. Neuroscience 303, 42–50.
Liu, X.Y., Wang, L.X., Chen, Z., Liu, L.B., 2016. Liraglutide prevents beta-amyloid-induced neurotoxicity in SH-SY5Y cells via a PI3K-dependent signaling pathway. Neurol. Res. 38 (4), 313–319.
LoBue, C., Munro, C., Schaffert, J., Didehbani, N., Hart Jr, J., Batjer, H., Cullum, C.M., 2019. Traumatic brain injury and risk of long-term brain changes, accumulation of pathological markers, and developing dementia: a review. J. Alzheimer'S. Dis. 70 (3), 629–654.
Lopes, C., Ribeiro, M., Duarte, A.I., Humbert, S., Saudou, F., Pereira de Almeida, L., Rego, A.C., 2014. IGF-1 intranasal administration rescues Huntington's disease phenotypes in YAC128 mice. Mol. Neurobiol. 49 (3), 1126–1142.
MacDonald, P.E., El-Kholy, W., Riedel, M.J., Salapatek, A.M.F., Light, P.E., Wheeler, M. B., 2002. The multiple actions of GLP-1 on the process of glucose-stimulated insulin secretion. Diabetes 51 (suppl_3), S434–S442.
Madathil, S.K., Carlson, S.W., Brelsfoard, J.M., Ye, P., D'Ercole, A.J., Saatman, K.E., 2013. Astrocyte-specific overexpression of insulin-like growth factor-1 protects hippocampal neurons and reduces behavioral deficits following traumatic brain injury in mice. PloS One 8 (6), e67204.
Mairet-Coello, G., Tury, A., DiCicco-Bloom, E., 2009. Insulin-like growth factor-1 promotes G1/S cell cycle progression through bidirectional regulation of cyclins and cyclin-dependent kinase inhibitors via the phosphatidylinositol 3-kinase/Akt pathway in developing rat cerebral cortex. J. Neurosci. 29 (3), 775–788.
Makkonen, I., Kokki, H., Kuikka, J., Turpeinen, U., Riikonen, R., 2011. Effects of fluoxetine treatment on striatal dopamine transporter binding and cerebrospinal fluid insulin-like growth factor-1 in children with autism. Neuropediatrics 42 (05), 207–209.
Martin, B., Chadwick, W., Cong, W.N., Pantaleo, N., Daimon, C.M., Golden, E.J., Maudsley, S., 2012. Euglycemic agent-mediated hypothalamic transcriptomic manipulation in the N171–82Q model of Huntington disease is related to their physiological efficacy. J. Biol. Chem. 287 (38), 31766–31782.
Masrori, P., Van Damme, P., 2020. Amyotrophic lateral sclerosis: a clinical review. Eur. J. Neurol. 27 (10), 1918–1929.
Masters, M.C., Morris, J.C., Roe, C.M., 2015. "Noncognitive" symptoms of early Alzheimer disease: a longitudinal analysis. Neurology 84 (6), 617–622.
Mayfield, K., Siskind, D., Winckel, K., Hollingworth, S., Kisely, S., Russell, A.W., 2015. Treatment of clozapine-associated obesity and diabetes with exenatide (CODEX) in adults with schizophrenia: study protocol for a pilot randomised controlled trial. BJ Psych Open 1 (1), 67–73.
McClean, P.L., Hölscher, C., 2014a. Liraglutide can reverse memory impairment, synaptic loss and reduce plaque load in aged APP/PS1 mice, a model of Alzheimer's disease. Neuropharmacology 76, 57–67.
McClean, P.L., Hölscher, C., 2014b. Lixisenatide, a drug developed to treat type 2 diabetes, shows neuroprotective effects in a mouse model of Alzheimer's disease. Neuropharmacology 86, 241–258.
McClean, P.L., Parthsarathy, V., Faivre, E., Hölscher, C., 2011. The diabetes drug liraglutide prevents degenerative processes in a mouse model of Alzheimer's disease. J. Neurosci. 31 (17), 6587–6594.
McColgan, P., Tabrizi, S.J., 2018. Huntington's disease: a clinical review. Eur. J. Neurol. 25 (1), 24–34.
McGovern, S.F., Hunter, K., Hölscher, C., 2012. Effects of the glucagon-like polypeptide-1 analogue (Val8) GLP-1 on learning, progenitor cell proliferation and neurogenesis in the C57B/16 mouse brain. Brain Res. 1473, 204–213.
Mehrabi, N.F., Waldvogel, H.J., Tippett, L.J., Hogg, V.M., Synek, B.J., Faull, R.L., 2016. Symptom heterogeneity in Huntington's disease correlates with neuronal degeneration in the cerebral cortex. Neurobiol. Dis. 96, 67–74.
Mueller, P.L., Pritchett, C.E., Wiechman, T.N., Zharikov, A., Hajnal, A., 2018. Antidepressant-like effects of insulin and IGF-1 are mediated by IGF-1 receptors in the brain. Brain Res. Bull. 143, 27–35.
Muller, C., Cheung, N.W., Dewey, H., Churilov, L., Middleton, S., Thijs, V.,. & Bladin, C. (2018). Treatment with exenatide in acute ischemic stroke trial protocol: A prospective, randomized, open label, blinded end-point study of exenatide vs. standard care in post stroke hyperglycemia.
Nadeem, A., Ahmad, S.F., Al-Harbi, N.O., Attia, S.M., Alshammari, M.A., Alzahrani, K.S., Bakheet, S.A., 2019. Increased oxidative stress in the cerebellum and peripheral immune cells leads to exaggerated autism-like repetitive behavior due to deficiency of antioxidant response in BTBR T+ tf/J mice. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 89, 245–253.
Nagano, I., Shiote, M., Murakami, T., Kamada, H., Hamakawa, Y., Matsubara, E., Abe, K., 2005. Beneficial effects of intrathecal IGF-1 administration in patients with amyotrophic lateral sclerosis. Neurol. Res. 27 (7), 768–772.
Naia, L., Ferreira, I.L., Cunha-Oliveira, T., Duarte, A.I., Ribeiro, M., Rosenstock, T.R., Rego, A.C., 2015. Activation of IGF-1 and insulin signaling pathways ameliorate mitochondrial function and energy metabolism in Huntington's Disease human lymphoblasts. Mol. Neurobiol. 51 (1), 331–348.
Nakazaki, M., Crane, A., Hu, M., Seghers, V., Ullrich, S., Aguilar-Bryan, L., Bryan, J., 2002. cAMP-activated protein kinase-independent potentiation of insulin secretion by cAMP is impaired in SUR1 null islets. Diabetes 51 (12), 3440–3449.
Negarandeh, Z., Mohamadzadeh Salamat, K., Hosseini, S.A., Etemad, Z., 2019. The effect of endurance training with crocin consumption on IGF-1 and glycogen expression in rat hippocampus tissue of trimethyltin-treated model of Alzheimer's disease. Asian J. Sports Med. 10 (3), e92246.
Nieto Guil, A.F., Oksdath, M., Weiss, L.A., Grassi, D.J., Sosa, L.J., Nieto, M., Quiroga, S., 2017. IGF-1 receptor regulates dynamic changes in neuronal polarity during cerebral cortical migration. Sci. Rep. 7 (1), 1–9.
Nieto-Estévez, V., Defterali, Ç., Vicario-Abejón, C., 2016. IGF-I: a key growth factor that regulates neurogenesis and synaptogenesis from embryonic to adult stages of the brain. Front. Neurosci. 10, 52.
Nizari, S., Basalay, M., Chapman, P., Korte, N., Korsak, A., Christie, I.N., Gourine, A.V., 2021. Glucagon-like peptide-1 (GLP-1) receptor activation dilates cerebral arterioles, increases cerebral blood flow, and mediates remote (pre) conditioning neuroprotection against ischaemic stroke. Basic Res. Cardiol. 116 (1), 1–13.

Ojaghihaghighi, S., Vahdati, S.S., Mikaeilpour, A., Ramouz, A., 2017. Comparison of neurological clinical manifestation in patients with hemorrhagic and ischemic stroke. World J. Emerg. Med. 8 (1), 34.
Okoreeh, A.K., Bake, S., Sohrabji, F., 2017. Astrocyte-specific insulin-like growth factor-1 gene transfer in aging female rats improves stroke outcomes. Glia 65 (7), 1043–1058.
Park, S.J., Lee, J.Y., Kim, S.J., Choi, S.Y., Yune, T.Y., Ryu, J.H., 2015. Toll-like receptor-2 deficiency induces schizophrenia-like behaviors in mice. Sci. Rep. 5 (1), 1–13.
Perini, G., Ramusino, M.C., Sinforiani, E., Bernini, S., Petrachi, R., Costa, A., 2019. Cognitive impairment in depression: recent advances and novel treatments. Neuropsychiatr. Dis. Treat. 15, 1249.
Pharaoh, G., Owen, D., Yeganeh, A., Premkumar, P., Farley, J., Bhaskaran, S., Logan, S., 2020. Disparate central and peripheral effects of circulating IGF-1 deficiency on tissue mitochondrial function. Mol. Neurobiol. 57 (3), 1317–1331.
Pini, G., Scusa, M.F., Congiu, L., Benincasa, A., Morescalchi, P., Bottiglioni, I., Tropea, D., 2012. IGF1 as a potential treatment for Rett syndrome: safety assessment in six Rett patients. Autism Res. Treat. 2012.
Pini, G., Congiu, L., Benincasa, A., DiMarco, P., Bigoni, S., Dyer, A.H., Tropea, D., 2016. Illness severity, social and cognitive ability, and EEG analysis of ten patients with Rett syndrome treated with mecasermin (recombinant human IGF-1). Autism Res. Treat. 2016.
Polinder, S., Cnossen, M.C., Real, R.G., Covic, A., Gorbunova, A., Voormolen, D.C., Von Steinbuechel, N., 2018. A multidimensional approach to post-concussion symptoms in mild traumatic brain injury. Front. Neurol. 9, 1113.
Puche, J.E., Muñoz, Ú., García-Magariño, M., Sádaba, M.C., Castilla-Cortázar, I., 2016. Partial IGF-1 deficiency induces brain oxidative damage and edema, which are ameliorated by replacement therapy. Biofactors 42 (1), 60–79.
Qi, L., Ke, L., Liu, X., Liao, L., Ke, S., Liu, X., Liu, L., 2016. Subcutaneous administration of liraglutide ameliorates learning and memory impairment by modulating tau hyperphosphorylation via the glycogen synthase kinase-3β pathway in an amyloid β protein induced alzheimer disease mouse model. Eur. J. Pharmacol. 783, 23–32.
Rachmany, L., Tweedie, D., Li, Y., Rubovitch, V., Holloway, H.W., Miller, J., Pick, C.G., 2013. Exendin-4 induced glucagon-like peptide-1 receptor activation reverses behavioral impairments of mild traumatic brain injury in mice. Age 35 (5), 1621–1636.
Rachmany, L., Tweedie, D., Rubovitch, V., Li, Y., Holloway, H.W., Kim, D.S., Pick, C.G., 2017. Exendin-4 attenuates blast traumatic brain injury induced cognitive impairments, losses of synaptophysin and in vitro TBI-induced hippocampal cellular degeneration. Sci. Rep. 7 (1), 1–13.
Ren, G., Xue, P., Wu, B., Yang, F., Wu, X., 2021. Intranasal treatment of lixisenatide attenuated emotional and olfactory symptoms via CREB-mediated adult neurogenesis in mouse depression model. Aging (Albany NY) 13 (3), 3898.
Ribeiro, M., Rosenstock, T.R., Oliveira, A.M., Oliveira, C.R., Rego, A.C., 2014. Insulin and IGF-1 improve mitochondrial function in a PI-3K/Akt-dependent manner and reduce mitochondrial generation of reactive oxygen species in Huntington's disease knock-in striatal cells. Free Radic. Biol. Med. 74, 129–144.
Rinderknecht, E., Humbel, R.E., 1978. The amino acid sequence of human insulin-like growth factor I and its structural homology with proinsulin. J. Biol. Chem. 253 (8), 2769–2776.
Rubin, J.B., Shia, M.A., Pilch, P.F., 1983. Stimulation of tyrosine-specific phosphorylation in vitro by insulin-like growth factor I. Nature 305 (5933), 438–440.
Russo, V.C., Gluckman, P.D., Feldman, E.L., Werther, G.A., 2005. The insulin-like growth factor system and its pleiotropic functions in brain. Endocr. Rev. 26 (7), 916–943.
Ruze, R., Xu, Q., Liu, G., Li, Y., Chen, W., Cheng, Z., Yan, Z., 2021. Central GLP-1 contributes to improved cognitive function and brain glucose uptake after duodenum-jejunum bypass on obese and diabetic rats. Am. J. Physiol. - Endocrinol. Metab. 321 (3), E392–E409.
Santi, A., Genis, L., Torres Aleman, I., 2018. A coordinated action of blood-borne and brain insulin-like growth factor I in the response to traumatic brain injury. Cereb. Cortex 28 (6), 2007–2014.
Sanz-Gallego, I., Rodriguez-de-Rivera, F.J., Pulido, I., Torres-Aleman, I., Arpa, J., 2014. IGF-1 in autosomal dominant cerebellar ataxia-open-label trial. Cerebellum Ataxias 1 (1), 1–9.
Sayed, N.H., Fathy, N., Kortam, M.A., Rabie, M.A., Mohamed, A.F., Kamel, A.S., 2020. Vildagliptin attenuates Huntington's disease through activation of GLP-1 receptor/PI3K/Akt/BDNF pathway in 3-nitropropionic acid rat model. Neurotherapeutics 17 (1), 252–268.
Scorza, F.A., do Carmo, A.C., Fiorini, A.C., Nejm, M.B., Scorza, C.A., Finsterer, J., Ferraz, H.B., 2017. Sudden unexpected death in Parkinson's disease (SUDPAR): a review of publications since the decade of the brain. Clinics 72, 649–651.
Scott, M.M., Williams, K.W., Rossi, J., Lee, C.E., Elmquist, J.K., 2011. Leptin receptor expression in hindbrain Glp-1 neurons regulates food intake and energy balance in mice. J. Clin. Investig. 121 (6), 2413–2421.
Seino, S., Shibasaki, T., 2005. PKA-dependent and PKA-independent pathways for cAMP-regulated exocytosis. Physiol. Rev. 85 (4), 1303–1342.
Selkoe, D.J., Hardy, J., 2016. The amyloid hypothesis of Alzheimer's disease at 25 years. EMBO Mol. Med. 8 (6), 595–608.
Serhan, A., Aerts, J.L., Boddeke, E.W., Kooijman, R., 2020. Neuroprotection by insulin-like growth factor-1 in rats with ischemic stroke is associated with microglial changes and a reduction in neuroinflammation. Neuroscience 426, 101–114.
Shandilya, A., Mehan, S., 2021. Dysregulation of IGF-1 and GLP-1 signaling in the progression of ALS: potential target activators and influences on neurological dysfunctions. Neurol. Sci. 42 (8), 3145–3166.
Shandilya, A., Mehan, S., Kumar, S., Sethi, P., Narula, A.S., Alshammari, A., Alasmari, A. F., 2022. Activation of IGF-1 and GLP-1 signalling via 4-hydroxyisoleucine prevents motor neuron impairments in experimental ALS-rats exposed to methylmercury-induced neurotoxicity. Molecules 27 (12), 3878.
Sharma, A., Mehan, S., 2021. Targeting PI3K-AKT/mTOR signaling in the prevention of autism. Neurochem. Int. 147, 105067.
Shiota, C., Larsson, O., Shelton, K.D., Shiota, M., Efanov, A.M., Høy, M., Magnuson, M.A., 2002. Sulfonylurea receptor type 1 knock-out mice have intact feeding-stimulated insulin secretion despite marked impairment in their response to glucose. J. Biol. Chem. 277 (40), 37176–37183.
Shofty, B., Bergmann, E., Zur, G., Asleh, J., Bosak, N., Kavushansky, A., Kahn, I., 2019. Autism-associated Nf1 deficiency disrupts corticocortical and corticostriatal functional connectivity in human and mouse. Neurobiol. Dis. 130, 104479.
Simsir, I.Y., Soyaltin, U.E., Cetinkalp, S., 2018. Glucagon like peptide-1 (GLP-1) likes Alzheimer's disease. Diabetes Metab. Syndr.: Clin. Res. Rev. 12 (3), 469–475.
Siskind, D.J., Russell, A.W., Gamble, C., Winckel, K., Mayfield, K., Hollingworth, S., Kisely, S., 2018. Treatment of clozapine-associated obesity and diabetes with exenatide in adults with schizophrenia: a randomized controlled trial (CODEX). Diabetes, Obes. Metab. 20 (4), 1050–1055.
Solmaz, V., Tekatas, A., Erdoğan, M.A., Erbaş, O., 2020. Exenatide, a GLP-1 analog, has healing effects on LPS-induced autism model: inflammation, oxidative stress, gliosis, cerebral GABA, and serotonin interactions. Int. J. Dev. Neurosci. 80 (7), 601–612.
Sun, J., Li, H., Jin, Y., Yu, J., Mao, S., Su, K.P., Liu, J., 2021. Probiotic Clostridium butyricum ameliorated motor deficits in a mouse model of Parkinson's disease via gut microbiota-GLP-1 pathway. Brain, Behav., Immun. 91, 703–715.
Sun, L., Grützner, C., Bölte, S., Wibral, M., Tozman, T., Schlitt, S., Uhlhaas, P.J., 2012. Impaired gamma-band activity during perceptual organization in adults with autism spectrum disorders: evidence for dysfunctional network activity in frontal-posterior cortices. J. Neurosci. 32 (28), 9563–9573.
Sun, L.Y., 2006. Hippocampal IGF-1 expression, neurogenesis and slowed aging: clues to longevity from mutant mice. Age 28 (2), 181–189.
Tai, J., Liu, W., Li, Y., Li, L., Hölscher, C., 2018. Neuroprotective effects of a triple GLP-1/GIP/glucagon receptor agonist in the APP/PS1 transgenic mouse model of Alzheimer's disease. Brain Res. 1678, 64–74.
Timper, K., del Río-Martín, A., Cremer, A.L., Bremser, S., Alber, J., Giavalisco, P., Brüning, J.C., 2020. GLP-1 receptor signaling in astrocytes regulates fatty acid oxidation, mitochondrial integrity, and function. Cell Metab. 31 (6), 1189–1205.
Toth, P., Tarantini, S., Ashpole, N.M., Tucsek, Z., Milne, G.L., Valcarcel-Ares, N.M., Ungvari, Z., 2015. IGF-1 deficiency impairs neurovascular coupling in mice: implications for cerebromicrovascular aging. Aging Cell 14 (6), 1034–1044.
Troubat, R., Barone, P., Leman, S., Desmidt, T., Cressant, A., Atanasova, B., Camus, V., 2021. Neuroinflammation and depression: a review. Eur. J. Neurosci. 53 (1), 151–171.
Tweedie, D., Rachmany, L., Rubovitch, V., Lehrmann, E., Zhang, Y., Becker, K.G., Pick, C. G., 2013. Exendin-4, a glucagon-like peptide-1 receptor agonist prevents mTBI-induced changes in hippocampus gene expression and memory deficits in mice. Exp. Neurol. 239, 170–182.
Tweedie, D., Rachmany, L., Rubovitch, V., Li, Y., Holloway, H.W., Lehrmann, E., Greig, N.H., 2016. Blast traumatic brain injury–induced cognitive deficits are attenuated by preinjury or postinjury treatment with the glucagon-like peptide-1 receptor agonist, exendin-4. Alzheimer's Dement. 12 (1), 34–48.
Valdeolivas, S., Navarrete, C., Cantarero, I., Bellido, M.L., Muñoz, E., Sagredo, O., 2015. Neuroprotective properties of cannabigerol in Huntington's disease: studies in R6/2 mice and 3-nitropropionate-lesioned mice. Neurotherapeutics 12 (1), 185–199.
Van Kesteren, C.F.M.G., Gremmels, H., De Witte, L.D., Hol, E.M., Van Gool, A.R., Falkai, P.G., Sommer, I.E.C., 2017. Immune involvement in the pathogenesis of schizophrenia: a meta-analysis on postmortem brain studies. Transl. Psychiatry 7 (3) e1075-e1075.
Venkatasubramanian, G., Chittiprol, S., Neelakantachar, N., Shetty, T., Gangadhar, B.N., 2010. Effect of antipsychotic treatment on Insulin-like Growth Factor-1 and cortisol in schizophrenia: a longitudinal study. Schizophr. Res. 119 (1–3), 131–137.
Ventorp, F., Bay-Richter, C., Nagendra, A.S., Janelidze, S., Matsson, V.S., Lipton, J., Brundin, L., 2017. Exendin-4 treatment improves LPS-induced depressive-like behavior without affecting pro-inflammatory cytokines. J. Park. Dis. 7 (2), 263–273.
Vogel, T., 2013. Insulin/IGF-signalling in embryonic and adult neural proliferation and differentiation in the mammalian central nervous system. Trends Cell Signal. Pathw. Neuron Fate Decis. 38–73.
Weina, H., Yuhu, N., Christian, H., Birong, L., Feiyu, S., Le, W., 2018. Liraglutide attenuates the depressive-and anxiety-like behaviour in the corticosterone induced depression model via improving hippocampal neural plasticity. Brain Res. 1694, 55–62.
White, M.F., 2014. IRS2 integrates insulin/IGF1 signalling with metabolism, neurodegeneration and longevity. Diabetes Obes. Metab. 16 (S1), 4–15.
Wiggins, L.D., Rice, C.E., Barger, B., Soke, G.N., Lee, L.C., Moody, E., Levy, S.E., 2019. DSM-5 criteria for autism spectrum disorder maximizes diagnostic sensitivity and specificity in preschool children. Soc. Psychiatry Psychiatr. Epidemiol. 54 (6), 693–701.
Winkler, M., Biswas, S., Berger, S.M., Küchler, M., Preisendörfer, L., Choo, M., Géraud, C., 2020. Pianp deficiency links GABAB receptor signaling and hippocampal and cerebellar neuronal cell composition to autism-like behavior. Mol. Psychiatry 25 (11), 2979–2993.
Wu, F., Yang, L., Hang, K., Laursen, M., Wu, L., Han, G.W., Stevens, R.C., 2020. Full-length human GLP-1 receptor structure without orthosteric ligands. Nat. Commun. 11 (1), 1–10.
Wu, M.-K., Wang, C.-K., Bai, Y.-M., Huang, C.-Y., Lee, S.-D., 2007. Outcomes of obese, clozapine-treated inpatients with Schizophrenia placed on a six-month diet and physical activity program. Psychiatr. Serv. 58 (4), 544–550. https://doi.org/10.1176/appi.ps.58.4.544.

Wyant, K.J., Ridder, A.J., Dayalu, P., 2017. Huntington's disease—update on treatments. Curr. Neurol. Neurosci. Rep. 17 (4), 1–11.

Xu, L., Chen, W.F., Wong, M.S., 2009. Ginsenoside Rg1 protects dopaminergic neurons in a rat model of Parkinson's disease through the IGF-I receptor signalling pathway. Br. J. Pharmacol. 158 (3), 738–748. https://doi.org/10.1111/j.1476-5381.2009.00361.x.

Xu, Q., Liu, Y.Y., Wang, X., Tan, G.H., Li, H.P., Hulbert, S.W., Jiang, Y.H., 2018. Autism-associated CHD8 deficiency impairs axon development and migration of cortical neurons. Mol. Autism 9 (1), 1–17.

Yan, H., Mitschelen, M., Toth, P., Ashpole, N.M., Farley, J.A., Hodges, E.L., Sonntag, W. E., 2014. Endothelin-1-induced focal cerebral ischemia in the growth hormone/IGF-1 deficient Lewis Dwarf rat. J. Gerontol. Ser. A: Biomed. Sci. Med. Sci. 69 (11), 1353–1362.

Yang, C., Sui, G., Li, D., Wang, L., Zhang, S., Lei, P., Chen, Z., Wang, F., 2021. Exogenous IGF-1 alleviates depression-like behavior and hippocampal mitochondrial dysfunction in high-fat diet mice. Physiol. Behav. 229, 113236 https://doi.org/10.1016/j.physbeh.2020.113236.

Yang, W., Li, G., Cao, K., Ma, P., Guo, Y., Tong, W., Wan, J., 2020. Exogenous insulin-like growth factor 1 attenuates acute ischemic stroke-induced spatial memory impairment via modulating inflammatory response and tau phosphorylation. Neuropeptides 83 (August), 102082. https://doi.org/10.1016/j.npep.2020.102082.

Yang, Y., Zhang, J., Ma, D., Zhang, M., Hu, S., Shao, S., Gong, C.X., 2013. Subcutaneous administration of liraglutide ameliorates alzheimer-associated tau hyperphosphorylation in rats with type 2 diabetes. J. Alzheimer's Dis. 37 (3), 637–648. https://doi.org/10.3233/JAD-130491.

Yao, L., Guo, Y., Wang, L., Li, G., Qian, X., Zhang, J., Liu, G., 2021. Knockdown of miR-130a-3p alleviates spinal cord injury induced neuropathic pain by activating IGF-1/IGF-1R pathway. J. Neuroimmunol. 351, 577458.

Yu, Y.W., Hsieh, T.H., Chen, K.Y., Wu, J.C.C., Hoffer, B.J., Greig, N.H., Li, Y., Lai, J.H., Chang, C.F., Lin, J.W., Chen, Y.H., Yang, L.Y., Chiang, Y.H., 2016. Glucose-dependent insulinotropic polypeptide ameliorates mild traumatic brain injury-induced cognitive and sensorimotor deficits and neuroinflammation in rats. J. Neurotrauma 33 (22), 2044–2054. https://doi.org/10.1089/neu.2015.4229.

Yuan, H., Chen, R., Wu, L., Chen, Q., Hu, A., Zhang, T., Zhu, X., 2015. The regulatory mechanism of neurogenesis by IGF-1 in adult mice. Mol. Neurobiol. 51 (2), 512–522.

Yuan, Z., Li, D., Feng, P., Xue, G., Ji, C., Li, G., Hölscher, C., 2017. A novel GLP-1/GIP dual agonist is more effective than liraglutide in reducing inflammation and enhancing GDNF release in the MPTP mouse model of Parkinson's disease. Eur. J. Pharmacol. 812 (June), 82–90. https://doi.org/10.1016/j.ejphar.2017.06.029.

Yun, S.P., Kam, T.I., Panicker, N., Kim, S., Oh, Y., Park, J.S., Kwon, S.H., Park, Y.J., Karuppagounder, S.S., Park, H., Kim, S., Oh, N., Kim, N.A., Lee, S., Brahmachari, S., Mao, X., Lee, J.H., Kumar, M., An, D., Ko, H.S., 2018. Block of A1 astrocyte conversion by microglia is neuroprotective in models of Parkinson's disease. Nat. Med. 24 (7), 931–938. https://doi.org/10.1038/s41591-018-0051-5.

Zhang, H., Liu, Y., Guan, S., Qu, D., Wang, L., Wang, X., Li, X., Zhou, S., Zhou, Y., Wang, N., Meng, J., Ma, X., 2016. An orally active allosteric GLP-1 receptor agonist is neuroprotective in cellular and rodent models of stroke. PLoS One 11 (2), 1–16. https://doi.org/10.1371/journal.pone.0148827.

Zhang, H., Liu, Y., Cheng, L., Ma, X., Luo, X., 2021. Exendin-4 induces a novel extended effect of ischemic tolerance via crosstalk with IGF-1R. Brain Res. Bull. 169, 145–155.

Zhang, J., Yi, T., Cheng, S., Zhang, S., 2020. Glucagon-like peptide-1 receptor agonist Exendin-4 improves neurological outcomes by attenuating TBI- induced inflammatory responses and MAPK activation in rats. Int. Immunopharmacol. 86 (April), 106715 https://doi.org/10.1016/j.intimp.2020.106715.

Zhang, L., Zhang, L., Li, L., Hölscher, C., 2018. Neuroprotective effects of the novel GLP-1 long acting analogue semaglutide in the MPTP Parkinson's disease mouse model. Neuropeptides 71 (July), 70–80. https://doi.org/10.1016/j.npep.2018.07.003.

Zhao, B., Zheng, Z., 2017. Insulin growth factor 1 protects neural stem cells against apoptosis induced by hypoxia through Akt/mitogen-activated protein kinase/extracellular signal-regulated kinase (Akt/MAPK/ERK) pathway in hypoxia-ishchemic encephalopathy. Med. Sci. Monit.: Int. Med. J. Exp. Clin. Res. 23, 1872.

Zheng, W.H., Quirion, R., 2004. Comparative signaling pathways of insulin-like growth factor-1 and brain-derived neurotrophic factor in hippocampal neurons and the role of the PI3 kinase pathway in cell survival. J. Neurochem. 89 (4), 844–852.

Zheng, W.H., Kar, S., Dore, S., Quirion, R., 2000. Insulin-like growth factor-1 (IGF-1): a neuroprotective trophic factor acting via the Akt kinase pathway. Adv. Res. Neurodegener. 261–272.

Zhu, D.M., Yang, Y., Zhang, Y., Wang, C., Wang, Y., Zhang, C., Zhu, J., 2020. Cerebellar-cerebral dynamic functional connectivity alterations in major depressive disorder. J. Affect. Disord. 275, 319–328.