Review Article

Diabetes, neurodegenerative diseases, GLP-1 & surgery: evidence calls for exploration

Abstract

Introduction: As life expectancy increases, the burden of chronic degenerative diseases is more evident. Diabetes and neurologic conditions such as Alzheimer's, Parkinson's and Huntington's diseases are clear examples of such burden. This review explores the links between these conditions with the objective of considering alternative therapeutic approaches for neurodegenerative diseases.

Discussion: Several links between diabetes, insulin resistance, metabolic syndrome and neurodegenerative diseases have been found. Factors such as GLP1 play a key role in Diabetes as well as in the development of neurodegenerative diseases. The proposed pathways suggested to explain the benefits of bariatric surgery on neurodegenerative diseases, involve the incretin pathways. Evidence gathered suggests a neuroprotective effect, halting progression and even promoting the regression of neurodegenerative traits associated with AD, whilst bariatric surgery produces a sustained overproduction of GLP-1.

Conclusion: Through the modification such pathways, through pharmaceutical or surgical means, an important decrease in the progression of cognitive deficit, the characteristic features associated to neurodegenerative diseases or even the regression of both might be expected. Therefore we consider it necessary to explore the effects of bariatric surgery upon neurodegenerative diseases.

Keywords: Diabetes; Alzheimer's; Parkinson's; Huntington's; Incretin; Surgery; DM; Parkinson's disease; Alzheimer's disease

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Abbreviations: DM: Diabetes Mellitus; AD: Alzheimer's Disease; PD: Parkinson's Disease; HD: Huntington's Disease; INEGI: National Institute for Statistics and Geography; COPD: Chronic Obstructive Pulmonary Disease; GERD: Gastroesopagheal Reflux Disease; GLP-1: Glucagon Like Peptide 1; GLP-1r: Glucagon Like Peptide 1 Receptor; GLP-1A: Glucagon Like Peptide 1 Analogue; DPP4: Dipeptidyl Peptidase 4; MeSH: Medical Sub Headings; APP: Amyloid Precursor Protein; BACE1: Beta-site Amyloid Precursor Protein Cleaving Enzyme 1; BMI: Body Mass Index; AUC: Area Under Curve; CNS : Central Nervous System; GSK-3: Glycogen Sintase Kinase-3

Introduction

As medical technology advances, life expectancy increases at a rate similar to that of which is seen when observing the incidence of ailments typically seen in elder patients and associated to aging and to a sedentary lifestyle. In Mexico, as reported by the national institute for statistics and geography or INEGI, chronic diseases with a direct association with obesity hold the first places as causes of death (acute myocardial infarction, diabetes, chronic kidney disease, stroke, COPD). Diabetes holds the 9th place as a general cause for morbidity, under infectious diseases, GERD and hypertension, whilst Alzheimer's disease holds the seventh spot in mortality, under car accidents and the mentioned diseases.

Recently experimental and physiopathological evidence has piled up explaining the association between obesity, diabetes and neurodegenerative diseases such as Alzheimer's disease, Parkinson's

disease and Huntington's Chorea. More important is the fact that in animal models of Alzheimer's, management with medication acting upon incretin pathways (Glucagon like peptide 1 or GLP-1 agonists and dipeptidyl peptidase 4 or DPP4 inhibitors) has a neuroprotective effect and may delay progression of tissular damage at the histopathologic level characteristic to certain neurodegenerative diseases as well as it may improve performance in cognitive tests performed upon such models.

On another perspective, it has been proven that in many ways the most effective management for diabetes is surgery, through procedures devised to control the global obesity pandemic, which upon the better understanding of their mechanisms of action, have been modified to suit the diabetic patient, even when not obese. The mentioned discipline, metabolic surgery, is defined as the study of anatomic manipulation of the anatomy of the gastro intestinal tract to achieve changes in enterohormonal secretion in order to reach a specific goal. Several metabolic and bariatric procedures have demonstrated to live up to their positive impact on diabetes through an enhanced secretion of GLP-1. In sight of the presented evidence, it is necessary to consider different strategies which may improve the course of Alzheimer's disease, and other neurodegenerative diseases, through an enhanced secretion of GLP-1.

A non restrictive search through the US National Library of Medicine-National Institutes of Health Pub Med database was done; The MeSH (Medical Sub Headings) terms used were Glucagon-Like Peptide 1 and Alzheimers Disease. The search resulted in 46 results which were revised and the information and was synthesized.

The Second search was done using the MeSH terms Glucagon-Like Peptide 1 and Parkinson Disease, obtaining a single result. Finally a third search was done with the MeSH terms Glucagon-Like Peptide 1 and Huntington's Disease and a single result was again produced, both the second and third searches were analyzed and synthesized in a similar fashion to the first one. In needed cases, reference considered appropriate was consulted.

Discussion

Alzheimer's, Parkinson's and huntigton's diseases

As population ages the prevalence of neurodegenerative diseases such Alzheimer's and Parkinson's diseases, stroke as well as other central nervous system diseases, increases. It is estimated that in 2030 the number of people living with Alzheimer's disease (AD) will reach 65.7 million.

Alzheimer's disease is the most common form of dementia and the most common form of cognitive disability. Less than 1% of the cases of AD have a genetic cause, while the great majority may have a multifactorial cause. Key features of AD such as loss of memory and cognitive capacity are associated with the increased deposit of B-amyloid, which is deposited in the form of plaques and neurofibrillary tangles of tau protein, this increase in B-amyloid deposition leads to a lack of stability of neuronal structures in the hippocampus.

There are three stages described in the development of AD. During the preclinical stage, B-amyloid is accumulates and causes early neurodegeneration and mild cognitive symptoms. The next stage is characterized by prodromic mild cognitive disfunction, and the last stage is AD dementia. Evidence suggests that anomalous Tau protein is passed from cell to cell and thus the anomalous Tau protein spreads throughout the brain cortex, while B-amyloid starts its accumulation in the outer cortex and then spreads to other areas. The relationship between the severity of AD and Tau protein density suggests that Tau protein could be the main cause for the loss of memory in patients with AD.

There are links in physiopathology between AD and diabetes. Insulin has diverse effects on various pathways of the central nervous system and may regulate several cognitive functions affected by AD. Insulin acts as a neuronal growth factor, promoting neuronal repair, dendritic growth and differentiation.[1] Alterations in insulin signal pathways and insulin resistance in the central nervous system play an important role in the pathogenesis of AD.[2] Insulin resistance in neurons has been described as an early manifestation of AD and is linked to cognitive loss. Insulin resistance develops as Insulin receptors and Insulin Receptor Substrate-1 (IRS-1) become scarce and malfunction.[3] The inhibition through phosphorylation of the serine residue on IRS-1 happens due to the effect of inflammatory cytokines produced by microglia in response to B-amyloid polymers,[4] which then build up in extracellular plaques in the brain cortex, which is related to an increase in amyloid precursor protein (APP) levels and beta-site amyloid precursor protein cleaving enzyme 1 (BACE1). The inhibition of the insulin signal pathway may favor the intracellular accumulation of B-amyloid and the phosphorylation of Tau. Normal Tau polymers and amyloid oligomers are cytotoxic and may impair cognitive function. Even though premature cellular degeneration is evident in both diseases, GLP-1 has been proven to reduce B-amyloid levels and to improve performance on cognitive tests performed on animal models.[5,6]

In Parkinson's disease (PD) there is an important loss of neurons at the pars compacta of the substantia nigra, which results in bradykinesia, resting tremor, stiffness and gait instability. There is also an important decline in Brain Derived Neurotropic Factor (BDNF), which is related to the development of dopaminergic neurons at the substantia nigra.

Leptin and Ghrelin, hormones involved in the development of obesity play a key role in the pathogenesis of PD, in murine models in which a ghrelin or a ghrelin receptor deficiency was induced, a loss of dopaminergic neurons could be observed. The relationship between PD and diabetes is less clear than in AD, nevertheless in murine models with Streptozotocin induced diabetes, lower levels of dopamine transporter mRNA and lower levels of thyroxin hydroxilase mRNA were found in the substantia nigra as well as proof of insulin resistance in the striate nucleus of PD.

Huntington's disease (HD) is a deadly neurodegenerative condition which presents with choreic movements, dystonia, cognitive and psychiatric dysfunctions. Microscopically, important cellular loss has been noticed in the caudate nucleus and the putamen. The genetic alteration produces a mutant form of the huntingtin protein which promotes cytotoxicity through a pathologic pathway of proteolysis and a diminished BDNF level. In a similar fashion to AD, in HD, there is an association with diabetes. An early trait of the disease is glycosuria and insulin resistance, whereas the management of the hyperglycemia is key in the management of the disease. The misbalance in glucose metabolism can be explained as the anomalous huntingtin favors the inhibition of the hypothalamic receptors for insulin by inhibitors of Phosphoinositide 3-kinase, resulting in hepatic insulin resistance and a rise in hepatic glucose production. Management with insulin does not correct such anomalies, while management with a GLP1 analogue, exendin 4, results in substantial improvements to glucose homeostasis and reduces the number of anomalous huntingtin deposits at the brain and pancreas leading to an increased lifespan in a murine model of HD.[7]

Diabesity

There are some supporting observations in which a mediterranean diet or a hypocaloric diet and intense physical activity have a protector effect against AD. Also, as explained by common metabolic alterations, global energetic balance and regulation and physical activity, the risk of cancer increases with the body mass index (BMI) in patients between ages 30 to 50.

Diabetes Mellitus (DM) is defined as a group of diseases which share the characteristic of hyperglycemia due to an inappropriate insulin secretion, insulin resistance or both. DM has become one of the greatest causes for mortality and morbidity in the world. Far from controlling its prevalence, the actual figures on incidence and prevalence have exceeded any prediction. It is estimated that by 2030 there will be more than 500 million patients living with diabetes in the world. The initial Rotterdam study demonstrated that type 2 diabetes increases the risk of developing dementia, while the risk was increased fourfold if the patient required insulin. The Rotterdam study suggested that insulin resistance is involved with an increased risk of developing AD upon 3 years of its appearance. Other studies suggest that Diabetes worsens overall prognosis and increases the risk of developing AD as much as 2-5 times, additionally it has been considered that hyperglycemia and hyperinsulinemia may be responsible for the development of AD. The relationship is so intricate, that some authors have considered calling AD 'type 3 diabetes', while others consider

that AD is a neuronal form of Reaven's insulin resistance syndrome characterized by insulin resistance, dyslipidemia, a pro inflammatory state and endotelial dysfunction.[8]

Diabesity and neurodegenerative diseases in the hispanic patient

A recent study analyzing in patients with AD in several ethnic groups determined that the ApoEε4 genotype is associated with AD in all ethnic groups. The Mexican American ethnic group at the Texas Alzheimer's Research and Care Consortium (TARCC) has been associated with hyperinsulinemia and diabetes. The most important marker was the fatty acid binding protein, involved in the fixation, transport and intracellular metabolism of long chain fat acids, which have also been linked to the development of diabetes, obesity, insulin resistance and metabolic syndrome. C reactive protein, GLP-1 and the pancreatic polypeptide were also involved in the development of insulin resistance.[9] It is therefore evident that in patients with Mexican ancestry the development of AD is linked to diabesity and metabolic syndrome.

GLP-1

Glucagon Like Peptide-1 (7-36) amide (GLP-1) is a enterohormone made up by 30 amino acids produced by terminal ileum and proximal colon's L cells. GLP-1 is 100% analogue in all mammals and is highly homologous among inferior vertebrates, which suggests a physiological importance. As mentioned before, its bioactive form is the GLP-1 (7-36) amide, which is known for its activity as an incretin when coupling with the GLP-1 receptor (GLP-1r) at the pancreatic B cells, though the activation the cyclic AMP pathway. When GLP-1 binds to GLP-1r it stimulates B cell proliferation, it inhibits apoptosis, favors glucose mediated insulin secretion, achieving glucose homeostasis, lowering food intake. Other functions of GLP-1 include the reduction in glucagon secretion, the inhibition of gastrointestinal motility, the inhibition of hepatic glucose production and release, inhibition of overall gluconeogenesis and glucogenolysis, acting at hypothalamic level to reduce appetite and increasing sensitivity to insulin, among others.[10]

Secretion of GLP 1 is mediated by glucose intake and fatty acids which interact with L cell receptors, gustducin or the TGR5 receptor. Its half life is short (less than 2 minutes) and it is metabolized by DPP-4 to GLP-1 (9-36) amide. While this form of GLP-1 was considered to be inactive, and it is as to its effects on insulin and glucose metabolism, it prevents the production of superoxide, protects the myocardium and reduces the inflammatory response in the hippocampus while limiting harm to synaptic function and memory in murine models of AD. Still, GLP-1 (9-36) amide has no activity on B-amyloid or APP.[11]

Important differences have been described when comparing area under curve (AUC) of GLP-1 concentrations in normal patients, those with glucose intolerance and diabetes mellitus, while DPP-4 concentrations are similar among the mentioned groups, which suggests that the shift in GLP-1 concentrations is not due to an increase in degradation,[12] being this statement highly controversial.[13] Recently, the ADDITION PRO study demonstrated important differences in GLP-1 secretion in pre diabetic patients, diabetic compared to healthy patients in response to a glucose tolerance trial. When grouped according to BMI, differences were observed on GLPP-1 secretion in healthy, overweight and obese patients, which might explain the association between the BMI, diabetes and AD.

The distribution of GLP-1 in the central nervous system (CNS) of rodents and humans has been related to the central control of appetite. Nevertheless there is evidence that links GLP-1r to an increase in neuronal plasticity, as well as to neuronal survival, protecting the organism from oxidative stress, B-amyloid, glutamate induced neuronal death, excitotoxicity, apoptosis as well as promoting dendritic growth.[14] Mice which over express GLP-1r demonstrate differences in learning compared to those in which GLP-1r is knocked out, who lack neuropcrotecive effects.

Optimal control of diabetes can reduce the progression of cognitive deficits in patients with AD. The use of drugs such as rioglitazone, pioglitazone has demonstrated to have a positive impact upon cognition and memory in patients with mild to moderate AD. While metformin by itself increases the formation of B-amyloid, combined with insulin it enhances the effects of insulin in reducing amyloid levels.

Diabetes management with GLP-1 analogues (liraglutide and exendin 4) has neuroprotective effects. In several studies, apart from an enhancement in peripheral insulin signaling, as well as central, GLP-1 agonists minimize cellular loss and perhaps could recover cognitive capabilities in murine models of AD, PD, HD. These drugs have even proven to be useful to revert the sequels of mild traumatic lesions in murine models.[15,16] There are works in progress focused upon the potential effect of exendin 4 in the management of PD,[17] preliminary results suggest that stimulating GLP-1r may revert the neurotoxic injury, leading to a potential therapeutic role.[18]

Panax Ginseng, an element in the traditional management of diabetes has shown to be valuable as an aid in the recovery of cognitive functions, as well as an aid in the enhancement of physical capabilities. One of 30 ginsengosides contained in Panax Ginseng, Rb1, interacts with L cells and favors secretion of GLP-1 in a dose-dependent manner.[19]

Incretin analogues

Based on their mechanisms of action there are two classes of drugs which enhance GLP-1 activity, GLP-1r agonists (GLP-1A) and DPP-4 inhibitors, increasing GLP-1's half life. Following subsections contain a concise summary of the available evidence.

Experience on Models of AD with GLP-1 and GLP-1A

GLP-1 holds neurotropic capabilities and may reduce B-amyloid deposits in vivo. Ghrelin, another hormone involved in the development of obesity and overweight is poorly regulated in patients with AD, GLP-1 improves Ghrelin regulation. Though major differences in plasma levels of these hormones in patients with AD have not been determined,[20] their kinetics may be involved in the development of key traits to AD.

Experimental management with intraventricular implants of GLP-1 producing stem cells in murine models of AD showed regression of amyloid plaque and the suppression of glial and microglial responses.[21]

In streptozocin induced diabetic mice and AD, exendin-4 (exendin-4 or exenatide, EX4, is a long acting GLP-1 analog found in the venom of Heloderma suspectum-Gila monster) has demonstrated neuroprotective effects promoting cell survival in cells submitted to pro apoptoic stimuli. EX4 protected neurons exposed to hyperglycemia through activation of the P13 kinase as well as reducing oxidative stress.

After a 14 day treatment mice treated with EX4 demonstrated an improvement in learning capabilities and memory compared to placebo. Histopathological analysis confirmed a reduced rate pf TAU protein and a reduction in GSK-3 expression (Glycogen Sintase Kinase-3 (GSK-3) is considered a key kinase in the development of DM and AD).[22]

Several other GLP-1 analogs are known to cross the blood-brain barrier (liraglutide, lixisenatide and D-Ala2-GIP) and are related to a protective effect on memory integration, to improved synaptic plasticity, promote synaptic number, reduce amyloid plaques and levels of the soluble beta amyloid. Overall these drugs are also related to a reduced chronic inflammatory response in the CNS.[23]

In murine models of AD and DM there some positive effects were observed when a course of subcutaneous liraglutide was administrated. Among these were lower cephaloraquideal insulin concentrations, lower Tau phosphorilation, lower protein kinase B and GKS-3 which were associated with a reduction in insulin signaling and improvement in observed brain abnormalities.[24] In other models, liraglutide has shown to reduce up to 33% the amyloid plaque deposit, a reduction in chronic inflammatory process even an increase in the number of neuronal stem cells at the dentatum gyrus by up to 50%, it also improved synaptic concentration at the cortex and hippocampus.[25] Clinical implications of these observations were demonstrated with an 8 week treatment to murine models APP/PS1 in which memory deficit was reduced, synaptic loss and the deleterious effects of AD in synaptic plasticity at the hippocampus were limited. Upon analysis, a 50% reduction in amyloid plaque was observed including an important reduction in microglial inflammation indexes.[26] Liraglutide was shown to favor neurogenesis by promoting cellular proliferation in AD, to affect stem cells that later on differentiate into neurons as demonstrated by the APP/PS1 murine model, this was also observed during chronic management and among different ages, opening the possibility to improve neurodegenerative disorders once diagnosed.[27]

Liraglutide treatment has demonstrated to prevent memory deficit, synaptic loss, reduce the number of beta amyloid plaques, reduce levels of beta amyloid precursor protein, reduce Tau protein hyperphosphorilation, favor glycosilation of cytoskeletal proteins, improve the JNK and ERK signal pathways reducing neuronal degeneration translating in a better cognitive performance, better learning capacity and reduced memory loss in mice.[28-30]

DPP-4 inhibitors

The active form of GLP-1, GLP-1 (7-36) amide is metabolized by the enzyme DPP-4 to GLP-1 (9-36) amide, hormone which seems to have no effect upon glucose or insulin metabolism.

The build up and accumulation of B-amyloid clusters is believed to be important in the development of cognitive deficit characteristic to AD. According to its biochemical composition, alanine is the penultimate residue con the N-terminal chain of B-amyloid, which leads to the theory that this residue is the site targeted by DPP-2 and DPP-4. The action of such enzymes could interrupt the formation and aggregation of B-amyloid plaques. This theory has been tested and confirmed by using B-amyloid 40 and 42 as substrate for DPP-4, inhibiting the formation of tangles and promoting its dissolution.[31]

Models treated with DPP-4 inhibitors show an increase in serum levels of GLP-1 (7-36) amide, increasing its effects upon the B-cell and the liver up to three times compared to organisms not receiving treatment.[32] On pigs, treated with Valine-Pyrrolidide, a stable DPP-4 inhibitor demonstrated a threefold increase of serum levels of GLP-1, while seeing a five-fold increase of serum GLP-1 after stimulation compared to the control group.[33] In such models treated with Valine-Pyrrolidide, GLP-1 had a life as much as three times longer than the control group. In murine models of streptozotocin induced AD, it was demonstrated that changes associated with AD were reverted depending on the dose and time of treatment with DPP-4 inhibitors, objectively demonstrating a reduced level of B-amyloid 42, lower Tau protein levels, phosphorylated Tau levels, neuroinflammation and an increase in GLP-1.[34]

Approved drugs (vildagliptine, saxagliptine) used on a daily basis on diabetes control have demonstrated similar effects. Examples of such effects are fewer B-amyloid deposits, reduced tau phosphorylation, reduced level of inflammatory markers and higher levels of GLP-1 as well as improved cognitive performance and histopathological findings in CNS tissue.[35,36] Linagliptine has also demonstrated neuroprotective effects, achieved through an increase in GLP-1 serum levels in murine models.[37,38]

Surgery for diabetes controls an Alzheimer's disease?

Obesity with or without diabetes is associated with a cognitive deficit and a high risk for developing dementia. The positive effect of the effective control of weight and glycemia can be explained through shared physiopathological pathways.[39] Bariatric surgery has demonstrated to lead to a moderate improvement in some of the cognitive deficits presented by obese patients.[40] Surgery has also proven to be the effective tool to achieve the remission of diabetes mellitus by promoting weight loss and through hormonal manipulation.[41]

Along with the rising prevalence of obesity, there is a significant number of neurodegenerative diseases such as AD and PD which have become more common. Evidence shows that 6 months after a gastric bypass, there is a significant reduction in the expression of mRNA linked to APP, presenilin-2, ADAM-9, GSK-3B, PICALM, SORL-1 and clusterin besides an important clinical improvement of cognitive capabilities of patients who have undergone bariatric surgery.[42] Patients that undergo gastric bypass have a reduced risk of coronary disease, peripheral angiopathy, stroke, diabetic nephropathy, peripheral neuropathy[43,44] as well as diabetic retinopathy.[45] In the case of nephropathy,[46] an improvement on the tissular damage and overall function markers has been observed, which has allowed for replacement therapy to be interrupted or delayed temporarily.[47]

The main actors in metabolic control and the reversion of complications could be the elevated concentrations of GIP, GLP-1 and PYY, resulting from an early contact between the L cell and raw nutrients[48-50] as well as the interaction between biliary salts and pancreatic juices, all which are promoted by procedures such as biliary pancreatic derivation, gastric bypass,[51] duodeno-jejunal bypass[52] and adaptive enterectomy. Although it was considered a mixed procedure (restrictive and malabsorptive), in gastric bypass the malabsoptive component seems to contribute to only 11% of the overall decrease in energetic absorption,[53] suggesting that it holds its main activity as a metabolic procedure.

The kinetics of the implied gut hormones has been studied in patients who have undergone a bypass surgery with gastrostomy, which showed substantial differences in insulin, GLP-1, GIP levels,

with increases in factors of 4.6, 1 and 2 respectively compared to serum levels of control groups.[54] The mentioned effects over GLP-1 secretion are maintained 5 years after surgery, and further.[55,56] Another path way by which serum levels of GLP-1 and PYY increase, is a noted hyperplasia and hypertrophy of L cells observed after gastric bypass.[57,58] Recent evidence suggests that the metabolic effects of gastric bypass (improvement in nitric oxide availability, reduced oxidative stress, HDL disfunction, reduced endothelial disfunction, anti inflammatory effects, antiapoptotic and antioxidant effects) were reversed when using a GLP-1 antagonist (exendin 9-39) as well as observing the same metabolic effects when increasing GLP-1 levels in rats without surgery through the administration of intravenous liraglutide.[59]

Evidence also suggests that the fact of promoting higher and more stable concentrations of GLP-1 produces an important improvement in B cell function, as well as an overall increase in B cell mass,[60] while these observations have not been confirmed in humans, the hyperinsulinemic hypoglycemia syndrome following gastric bypass has been suggested as a period of hyperactivity/hyperplasia of B cells due to GLP-1, and that can be reverted with the use of exendin (9-39).[61-63] Nevertheless, there is evidence which yields the past statements controversial.[64]

Other procedures such as ileal transposition, jejunectomy and duodenojejual bypass are based on the concept of promoting the early exposition of raw nutrients to the terminal ileon, stimulating L cells and promoting incretin activity as well as that of other gut hormones,[65,66] reversing kidney damage in murine models with diabetes.[67] The physiological substrate is to promote the secretion of GLP-1 and to avoid exposure of nutrients to the duodenum and jejunum, avoiding the expression of an anti-incretin factor, nevertheless, no difference was shown in animal models comparing duodenojejual bypass and jejunectomy.[68]

Restrictive procedures such as vertical gastrectomy favor changes in the incretin system, possibly through vagal afferent manipulation as this technique does not favor the early exposition of the distal gut, like other techniques (bypass, biliopancreatic derivation).[69] Procedures involving no resection, such as gastric plication have demonstrated to favor weight loss with an improved glycemic control and an elevated GIP, without changing GLP-1 concentrations, which suggest that the mechanic event of afferent pathway dissension isn't enough to alter GLP-1 kinetics, explaining its positive effects on diabetes and AD.

Prospects

Overall, evidence suggests that an increase in GLP-1, weight loss and the protection of incretin pathways have a favorable effect on cognitive deficits and may aid in the treatment of AD, PD and perhaps HD. While the cost, ethical implications, the complexity of a long term follow up in human protocols may hinder the development of large cohorts that would provide a reliable theoretical base to the use of surgery in the management of neurodegenerative disorders, the burden of disease does call for exploration. Several academic groups have suggested murine models might provide valuable information and there is communication with local experts regarding the possibility of a murine cohort to analyze the effect of microsurgery on murine AD models.

Conclusion

Evidence analyzed suggests that GLP-1 has neuroprotective effects and that it can effectively reduce progression and event solve certain anomalies which are characteristic to neurodegenerative diseases such as AD. The use of GLP-1A, as well as DPP4 inhibitors promote

there effects in vivo in murine models. Last, metabolic surgery promotes a state of increased GLP-1 production leading us to believe it is necessary to explore the effects of surgery on neurodegenerative diseases.

Conflicts of interest

The author declares there is no conflict of interest.

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