The Clinical Significance of Cyclic Glycine-Proline

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Cyclic Glycine-Proline and insulin-like growth factor binding protein (IGFBP)-3 collectively regulate the bioavailability of IGF-1. The molar ratio of cGP/IGF-1 represents the amount of bioavailable and functional IGF-1 in circulation. The cGP/IGF-1 molar ratio is low in patients with age-related conditions, including hypertension, stroke, and neurological disorders with cognitive impairment. Stroke patients with a higher cGP/IGF-1 molar ratio have more favorable clinical outcomes. The elderly with more cGP have better memory retention. An increase in the cGP/IGF-1 molar ratio with age is associated with normal cognition, whereas a decrease in this ratio with age is associated with dementia in Parkinson disease. In addition, cGP administration reduces systolic blood pressure, improves memory, and aids in stroke recovery. These clinical and experimental observations demonstrate the role of cGP in regulating IGF-1 function and its potential clinical applications in age-related brain diseases as a plasma biomarker for—and an intervention to improve—IGF-1 function.

cyclic glycine-proline

1. Introduction

The clinical relevance of cyclic Glycine-Proline (cGP) is in those conditions associated with Insulin-like growth factor-1 (IGF-1) deficiency, particularly the age related vascular diseases—metabolic hypertension, stroke, age-related cognitive decline, and some neurodegenerative disorders such as Parkinson's disease (PD) [1][2] and Alzheimer's disease (AD) [3][4][5]. Given the role of cGP in regulating IGF-1 function, it was evaluated that the changes in cGP, IGF-1, and IGFBP-3 concentrations in plasma and brain tissues, as well as their association with clinical outcomes in patients with metabolic hypertension, stroke, age-related cognitive impairment, PD, and AD. To support the interpretation of these clinical observations, the efficacy of cGP has been evaluated in animal models of metabolic disorders, stroke, memory impairment, and PD.

2. Hypertension

Obesity, dyslipidemia, hyperglycemia, and hypertension are collectively defined as metabolic syndrome, with a high risk of developing cardiovascular and cerebrovascular diseases [6] and dementia. IGF-1 plays an important role in energy metabolism [7][8]. IGF-1 deficiency is associated with obesity [9] and hypertension [10]. This age-related condition can also occur in a younger population, i.e., gestational hypertension. In healthy women, plasma concentration IGF-1 decreases transiently during early pregnancy due to growth hormone (GH) resistance, then

recovers after the women give birth, but it remains low in women with metabolic syndrome [11]. This difference provides a window of opportunity to evaluate whether cGP changes by responding to IGF-1 concentration in humans. A cross-sectional study compared the changes in plasma concentrations of cGP, IGF-1, and IGFBP-3 between healthy women and women with hypertension 6 years post-partum [11]. Plasma concentrations of IGFBP-3 and cGP are lower in hypertensive women compared to those with normal blood pressure, independent of obesity status [11]. The reduced plasma IGFBP-3 concentration is an endogenous response to improve the bioavailability of IGF-1, whereas the lowered plasma cGP can reduce the bioavailability of IGF-1 in circulation. To support this interpretation, the efficacy of cGP in a rat model of metabolic syndrome were examined. The rats develop metabolic syndrome after 8 weeks of high-fat diet feeding (HFD) during post-natal weeks 3–11 [12]. Compared to the group on the control diet, the HFD group shows an increase in systolic blood pressure (SBP), adiposity, and insulin insensitivity. As noted in the observations in women, HFD feeding decreases the concentrations of IGF-1 and IGFBP-3, whereas the cGP concentration increases in the plasma [12], this being a compensatory response to improve IGF-1 function. The administration of cGP from post-natal weeks 11–15 reduces the SBP and retroperitoneal fat weight, but not body weight and insulin resistance [12]. Correlation analysis shows that the rats with higher plasma cGP concentrations have a lower retroperitoneal fat weight, independent of the status of obesity. Endogenous concentration of cGP is positively correlated with SBP in saline-treated hypertensive rats [12], which could be an endogenous, but ineffective, response to improve IGF-1 function. With increasing plasma cGP concentration, via administration, hypertensive rats with higher cGP showed lower SBP [12]. This effect was not seen in normotensive rats [12]. Treatment with cGP that increases plasma cGP concentration leads to an effective response in normalizing blood pressure and retroperitoneal fat weight. These beneficial effects of cGP on SBP and retroperitoneal fat suggest a therapeutic potential for cGP in cardio-metabolic complications including, for example, stroke.

Hypertension is a life-long risk factor for stroke [13] and shares the pathology of endothelial dysfunction and the pathophysiology of impaired IGF-1 function [14]. The following section reviews the role of cGP in regulating IGF-1 function at the onset of stroke and during first 3 months of recovery as a neurological condition of vascular origin [15][16].

3. Stroke

The function of IGF-1 in stroke recovery has been well-documented [17]. Most stroke patients make a partial recovery in function within the first 3 months, a critical period for ‘self-made’ (i.e., spontaneous) recovery [18]. To investigate whether endogenous cGP is associated with this self-made recovery in stroke patients, plasma concentrations of cGP, IGF-1, and IGFBP-3 at the onset of stroke and 3 months post-stroke recovery were evaluated [14]. This longitudinal clinical study includes 50 non-stroke control participants and 34 stroke patients. The National Institutes of Health Stroke Scale (NIHSS) is assessed within three days of hospital admission (<3 days) as a baseline, and at days 7 and 90; the modified Rankin Scale (mRS) and Fugl-Meyer Upper-Limb Assessment Scale (FM-UL) are administered at days 7 and 90. Plasma samples were are also collected from patients at baseline, and days 7 and 90.

Compared with the control participants, the plasma concentrations of IGFBP-3 and cGP were lower in stroke patients at the time of hospital admission, and the concentration of IGF-1 was similar [14]. The reduction of plasma IGFBP-3 in stroke patients could be a positive response to increase the amount of bioavailable IGF-1 in the circulation, whereas the low plasma cGP suggests a reduction of bioavailable IGF-1 in circulation during the onset of stroke [14]. Multiple regression analysis after adjustment for potential confounding factors (age and baseline NIHSS scores [19]) suggests that the patients with a higher plasma concentration of cGP and/or molar ratio of cGP/IGF-1 at the time of hospital admission make a better recovery, with fewer neurological deficits at day 90 post-stroke.

Plasma concentrations of cGP and cGP/IGF-1 molar ratio increase over 90 days, in parallel with the improved motor function and clinical outcomes. However, the concentrations of IGF-1 and IGFBP-3 remain the same during the recovery phase [14]. Several groups have evaluated the changes in the plasma concentration of IGF-1 at 3 days after stroke, with inconsistent results [20][21]. Changes in plasma IGF-1 concentrations at the one-set of stroke appear to be associated with mortality, but not functional recovery [22]. This observation also supports the notion that changes in plasma IGF-1 concentrations are not associated with IGF-1 function during stroke recovery, whereas cGP-related changes (cGP/IGF-1 molar ratio) are [14]. This association between cGP/IGF-1 ratio and stroke recovery provides additional evidence for cGP as a regulator of IGF-1 function.

This idea is also supported by experimental studies. Intracerebroventricular administration of cGP (0.2 µg/rat, *i.c.v.*) 2 h after a unilateral hypoxic-ischemic brain injury partially reduces neuronal loss in the hippocampus, as compared to that noted in the control rats. In an analysis of capillary densities, almost complete vascular protection/restoration in the hippocampus after cGP treatment were found [23]. This treatment effect on vascular protection is in parallel to an increase in the phosphorylation of IGF-1 receptors in the capillaries [23]. The expression of IGF-1 receptors does not occur in the endothelial cells, but possibly on the pericytes [23], which play a key role in vascular remodelling through expressing angiogenic factors [24]. Taken together, the data suggest that the cGP-associated vascular protection is mediated through IGF-1. The treatment with cGP did not further increase vascular density in the control hippocampus, where there is no vascular damage [23]. The administration of a structural analogue of cGP six hours after the onset of stroke protects the brain from ischemic injury and improves long-term sensory-motor function [25].

Changes in the cGP/IGF-1 molar ratio may assist in the prediction of the clinical outcome and management of stroke [14]. The molar ratio of cGP/IGF-1 in plasma during the onset of stroke may be developed as a biomarker for predicting the ability of functional recovery in stroke patients. Considering the oral bioavailability and dynamic central uptake of cGP in humans [26], the development of this biomarker could provide guidance to assist future clinical trials in stroke.

Age-related cognitive impairment has been suggested as being associated with vascular degeneration and poor vascular function [27]. In the next section, the changes in the cGP/IGF-1 molar ratio in age-related cognitive status is reviewed.

4. Age-Related Cognitive Decline

Healthy vascular function is critical for maintaining normal cognition in humans [28][29]. Age-related cognitive decline is considered to be associated with the vascular ageing processes [27]. Aged rats show poor spatial memory compared to young rats in Morris Water Maze performance [27]. Stereological analysis shows that the neuronal density in the hippocampus is similar in young and aged rats [27]. Instead, the aged rats that show memory impairment have significantly fewer capillaries and glial cells, as well as a lower expression of synaptic markers in the hippocampus, than do the young rats [27]. These data suggest that age-related cognitive impairment is associated with neuronal dysfunction that is due, at least in part, to glial and vascular degeneration.

Vascular ageing contributes to cognitive decline in humans [30]. IGF-1 plays an essential role in the vascular remodeling of the adult brain [31] and supports the retention of normal cognition [32]. Age-related IGF-1 deficiency contributes to cognitive impairment in older people [32][33][34][35]. A recent observational study examined the association between plasma concentrations of IGF-1, IGFBP-3 and cGP and the cognitive scores in a group of older people (mean = 74.5 years of age) with normal cognitive function. Multiple regression analysis after adjustment for age shows that the cGP concentration and the cGP/IGF-1 molar ratio are positively associated with scores on the Montreal Cognitive Assessment (MoCA), a global measure of cognitive function derived from comprehensive neuropsychological testing (Global Z), and test scores in the learning and memory domain (LMD) [36]. In contrast, plasma concentration of IGF-1 and IGFBP-3 are not associated with these cognitive measures [36]. These data suggested that older people with higher plasma cGP concentrations and/or a higher cGP/IGF-1 molar ratio exhibit better learning and memory functions. An independent study observed an increase in the cGP/IGF-1 molar ratio and a decrease in the IGFBP-3 concentration in older people with mild cognitive impairment [37], suggesting an ineffective response to overcome age-related cognitive decline.

5. Parkinson’s Disease (PD)

Using immunohistochemical staining to visualize endothelial cells, Guan et al. first reported endothelial degeneration in human PD brains [38]. The loss of endothelial cells in the capillaries leads to the formation of string vessels with no function in cerebral circulation [39].

Vascular degeneration in older people and PD is associated with IGF-1 deficiency, which also impairs the vascularization processes [40]. Thus, vascular degeneration may be, at least partially, an age-related pathology which can potentially increase the risk of developing cognitive impairment in older people [41][42][43] and PD patients [33][44][45][46].

While plasma IGF-1 decreases with age [33], it is elevated in PD patients compared to non-PD controls [47][48][49]. This age effect confounds the PD effects on the IGF-1 concentration in circulation. To reveal the specific association of IGF-1, cGP, and IGFBP-3 with age, cognitive function, or motor deficits, the data are analyzed using a multiple linear regression model, with adjustment for age, motor, and cognitive scores accordingly. The analysis

suggested that the changes in the plasma concentration of IGF-1 and cGP with age are associated with cognitive status [36], and the changes in plasma IGFBP-3 concentrations are associated with motor deficits in PD.

The plasma concentration of IGF-1 decreases with age, whereas cGP increases with age in the PD patients with normal cognition (PD-N), leading to an age-related increase in the cGP/IGF-1 molar ratio [36]. This increase in the cGP/IGF-1 molar ratio is absent in the PD group with mild cognitive impairment (PD-MCI). In contrast, the cGP/IGF-1 molar ratio decreases with age in the PD group with dementia (PD-D). Compared with the PD-N group, the association regression slope of the cGP/IGF-1 molar ratio is reversed in the PD-D group. These data suggest that cognitive impairment in PD is age related, and the age effects on the cGP/IGF-1 molar ratio are differently associated with the cognitive status in PD [36].

An increase in the plasma cGP/IGF-1 molar ratio with age may contribute to the preserved cognitive function in the PD-N group, possibly due to the improvement in the amount of bioavailable IGF-1 in the plasma. In contrast, the decrease in the cGP/IGF-1 molar ratio with age in the PD-D group may reverse this effect during the progression to dementia. The static relationship between the cGP/IGF-1 molar ratio and age in the PD-MCI group could be a transition phase prior to dementia. These observations raise the possibility that the association between the cGP/IGF-1 molar ratio and age may assist in predicting cognitive status and the risk of advanced cognitive impairment in PD patients, but these hypotheses require further confirmation with longitudinal observations.

IGF-1 resistance, characterized as an increase in IGF-1 concentration, may contribute to the progression of motor deficits in PD. The same study that evaluated the cognitive status also examined the association of cGP, IGF-1, and IGFBP-3 with UPDRS, commonly used for evaluating motor deficits in PD patients. The IGF-1 concentration in plasma is higher in PD patients than in the non-PD controls, suggesting IGF-1 resistance in this cohort of patients. Multiple linear regression analysis after correction for age and 3 individual cognitive scores shows a positive correlation between UPDRS and the plasma concentration of IGFBP-3 (Table 1, unpublished data). The motor deficits in PD are not correlated with the cGP and IGF-1 concentrations.

Table 1. Correlation between plasma concentration of IGFBP-3 and motor deficits.

Dependent Variable		**cGP**	**IGF-1**	**IGFBP-3**
(Confounders)		**(ng/mL)**	**(ng/mL)**	**(ng/mL)**
UPDRS	B	−0.01	0.01	0.004
(Age and MoCA)	P	0.98	0.60	**0.02**
	95%CI	−0.50,	−0.03,	0.001,

		0.48	0.05	0.007
	B	0.20	0.004	0.004
UPDRS (Age and Global Z)	P	0.38	0.85	**0.02**
	95%CI	−0.25, 0.66	−0.04, 0.05	0.001, 0.007
	B	0.26	0.01	0.004
UPDRS (Age and LMD)	P	0.27	0.61	**0.01**
	95%CI	−0.21 0.72	−0.03 0.06	0.001 0.01

UPDRS: Movement Disorder Society Unified Parkinson's Disease Rating Scale; MoCA: Montreal Cognitive Assessment; LMD: learning memory domain scores; Global Z score: global measure of cognitive function derived from comprehensive neuropsychological testing.

High concentration of IGFBP-3 would increase IGFBP-3 binding to IGF-1 and reduce the amount of bioavailable IGF-1 in circulation. Given that only bioavailable IGF-1 can cross the blood–brain barrier, the reduction in bioavailable IGF-1 in plasma can also reduce the brain penetration of IGF-1, which is the main source of IGF-1 in brain tissues. Provided that cGP can displace IGF-1 from IGFBP-3 binding, increasing cGP through an intervention might also reduce IGF-1 resistance and increase the bioavailability of IGF-1 in circulation. Using immunohistochemistry, Yang et al. examined the expression of IGF-1 and IGFBP-2 in the brain regions of PD cases. Compared to non-PD cases, the expression of IGF-1 is reduced, whereas the expression of IGFBP-2, a main IGFBP, is increased in PD brain tissues [40]. The higher expression of IGFBP-2 is collocated with glial cells, suggesting an association with brain inflammation in PD [40].

6. Alzheimer's Disease (AD)

Vascular aging has been suggested to contribute to the progression, or even the cause, of AD [50], a neurodegenerative condition marked by cognitive impairment and dementia. Wang (2019) compares the changes in IGF-1, cGP, and IGFBP-3 between 15 patients with mild AD and 15 normal controls. The mean Addenbrookes Cognitive Examination (ACE-111) score is 94.21 ± 0.72 in cognitively healthy participants and 82.67 ± 1.45 in those who had a diagnosis of AD ($p < 0.001$). The mean value for the ACE-111 score in the AD patients suggests that their dementia status is relatively mild. Compared to non-AD controls, the AD patients exhibit an increase in cGP and a decrease in IGFBP-3 concentrations, while changes in IGF-1 are not significant [37]. These results also suggest a collective regulatory response between cGP and IGFBP-3 to maintain IGF-1 function and to slow down disease progression to dementia.

While the majority of bioavailable IGF-1 in brain tissues is transported from the circulation to brain tissues by the activation of IGF-1 receptors [51], a small amount is produced locally through glial cells, which themselves can be enhanced after brain injury [40][52]. Even though IGF-1 in brain tissues is more bioavailable than that in circulation, the reversible binding of IGF-1 to mainly IGFBP-2 also plays a role in influencing the bioavailability of IGF-1 in brain tissues. While cGP can be generated locally via IGF-1 metabolism in brain tissues, the majority of cGP is transferred across the blood–brain barrier (BBB) from circulation [12][26].

A recent human brain tissue study evaluated changes in IGF-1, cGP, and IGFBP-2 and -3 in the brain regions of AD cases and age-matched control cases [53]. The concentration of total IGF-1 is lower in the inferior-frontal gyrus and middle-frontal gyrus of the AD brains compared to the control brains. Vascular degeneration is a key pathological feature of AD [54]. As part of the structure and function of the BBB, the degeneration of capillaries in the AD brain [55] may reduce IGF-1 receptors, which are essential for central transfer of bioavailable IGF-1. Given the essential role of circulating IGF-1 in vascular remodeling [31][32], a deficiency of plasma IGF-1 can impact vascular remodeling and the function of the BBB in transferring IGF-1 from plasma to brain tissues.

In contrast, the concentrations of IGFBP-3 and cGP are higher in the inferior-frontal gyrus and middle-frontal gyrus in the AD compared to the control cases [53]. The increase in IGFBP-3 concentration, which could be a result of an inflammatory response to brain degeneration [56], may reduce bioavailable IGF-1 in the AD brain, further reducing the amount of bioavailable IGF-1. The increase in cGP is likely a response to improve the bioavailability of IGF-1 in the AD brain [53].

Given the anabolic effects of IGF-1 in the brain [57], the protein concentration could be an indication of IGF-1 function in brain. The authors analyzed the total protein concentration of the brain tissues used for analyzing cGP, IGF-1, and IGFBPs. The total protein concentration in AD brain tissues is lower [53] than in the controls, and is negatively associated with IGFBP-3 in AD cases. In contrast, the total protein concentration is associated with a decrease in IGF-1 concentration, but an increase in cGP concentration in the control cases. These observations suggest that IGF-1 function is deficient in the AD brain. The increase in IGFBP-3 in the AD brain could be the result of inflammation, and the increase in cGP could be a positive response to age-related decline in IGF-1. This interpretation is supported by other experimental observations [58][59]. High-fat diet feeding after weaning induces metabolic syndrome in rats, with reduced synaptic expression in the hippocampus and striatum [58]. The peripheral

administration of cGP increased the cGP concentration in brain tissues and normalized synaptic expression, without increasing IGF-1 concentration in the brain. Thus, the effects of cGP on synaptic function could be associated with an increase in bioavailable IGF-1 in the brain tissue [58]. Central administration of cGP reduces brain damage in rats with hypoxic-ischemic injury by activating the IGF-1 receptors [23]. Mediated through developmental programming, the memory improvement of adult offspring after maternal administration of cGP to lactating rat dams is associated with advancing astrocytic plasticity and vascular remodeling, leading to synaptic trafficking through the glutamine–glutamate cycle in the hippocampus [59][60]. Thus, the memory improvement associated with cGP intervention could be, in part, a vascular effect.

Vascular disease is a common risk factor contributing to cognitive impairment and stroke [61][62][63]. The normal function of IGF-1 is essential for cerebral vascular remodeling in mature brain and is mediated through the endothelium of cerebral vessels [31]. Given the association of vascular disease with the function of circulating IGF-1, a plasma biomarker for IGF-1 function would have clinical significance in assisting the assessment of the status and prognosis of vascular disease. Plasma concentrations of IGF-1 and the ratio of IGF-1/IGFBP-3 have been under clinical evaluation for their association with vascular diseases, i.e., age related cognitive status and stroke recovery [44][64][65]. The findings in this area have been mixed and difficult to interpret [44][64][65]. As discussed earlier, the majority of IGF-1 in plasma is not bioavailable, so it does not represent the functional impact of circulating IGF-1. The IGF-1/IGFBP-3 ratio could be a better representation of functional IGF-1 in circulation than IGF-1 alone, but more than 70% of circulating IGFBP-3 is independent of IGF-1. Given its association with age-related cognitive status and stroke recovery, changes in cGP/IGF-1 molar ratio and/or cGP concentration could be a better plasma biomarker to identify those at greater risk of cognitive decline and poor ability to recover from stroke.

The administration of cGP protects the rat brain from ischemic injury by promoting IGF-1-mediated vascular protection [23]. Similarly, cGP treatment normalizes systolic blood pressure in rats with metabolic disorders [12]. Given the existence of cerebral vascular degeneration/dysfunction in age-related cognitive impairment [27], the changes in plasma the cGP/IGF-1 molar ratio may be a biomarker for the identification of the window of opportunity for suitable intervention, monitoring treatment response, and individualizing medical treatment.

References

1. Kizza, J., S. Lewington, et al., Cardiovascular risk factors and Parkinson's disease in 500,000 Chinese adults. Ann Clin Transl Neurol, 2019. 6(4): p. 624-632.10.1002/acn3.732.
2. Xu, X., Z. Fu, et al., Exercise and Parkinson's disease. Int Rev Neurobiol, 2019. 147: p. 45-74.10.1016/bs.irn.2019.06.003.
3. Lu, X., M. Moeini, et al., Hypertension accelerates cerebral tissue PO(2) disruption in Alzheimer's disease. Neurosci Lett, 2020. 715: p. 134626.10.1016/j.neulet.2019.134626.

4. Morovic, S., H. Budincevic, et al., Possibilities of Dementia Prevention - It is Never Too Early to Start. J Med Life, 2019. 12(4): p. 332-337.10.25122/jml-2019-0088.
5. Solis, E., Jr., K.N. Hascup, et al., Alzheimer's Disease: The Link Between Amyloid-β and Neurovascular Dysfunction. J Alzheimers Dis, 2020. 76(4): p. 1179-1198.10.3233/jad-200473.
6. Srikanthan, K., A. Feyh, et al., Systematic Review of Metabolic Syndrome Biomarkers: A Panel for Early Detection, Management, and Risk Stratification in the West Virginian Population. Int J Med Sci, 2016. 13(1): p. 25-38.10.7150/ijms.13800.
7. Binoux, M., The IGF system in metabolism regulation. Diabete Metab, 1995. 21(5): p. 330-7.
8. Karmali, R., A. Dalovisio, et al., All in the family: Clueing into the link between metabolic syndrome and hematologic malignancies. Blood Rev, 2015. 29(2): p. 71-80.10.1016/j.blre.2014.09.010.
9. Savastano, S., C. Di Somma, et al., Liver-spleen axis, insulin-like growth factor-(IGF)-I axis and fat mass in overweight/obese females. J Transl Med, 2011. 16(9): p. 136-141.10.1186/1479-5876-9-136.
10. Schutte, A.E., M. Volpe, et al., Revisiting the relationship between blood pressure and insulin-like growth factor-1. Hypertension, 2014. 63(5): p. 1070-7.10.1161/hypertensionaha.113.03057.
11. Guan, J., G. Singh-Mallah, et al., The role for cyclic Glycine-Proline, a biological regulator of insulin-like growth factor-1 in pregnancy-related obesity and weight changes. J Biol Regul Homeost Agents, 2018. 32(3): p. 465-478.
12. Li, F., K. Liu, et al., Cyclic glycine-proline normalizes systolic blood pressure in high-fat diet-induced obese male rats. Nutr Metab Cardiovasc Dis, 2019.10.1016/j.numecd.2019.09.016.
13. Turin, T.C., T. Okamura, et al., Hypertension and lifetime risk of stroke. J Hypertens, 2016. 34(1): p. 116-22.10.1097/hjh.0000000000000753.
14. Fan, D., R. Krishnamurthi, et al., Plasma cyclic glycine proline/IGF-1 ratio predicts clinical outcome and recovery in stroke patients. Ann Clin Transl Neurol, 2019. 6(4): p. 669-677.10.1002/acn3.743.
15. Pires, P.W., C.M. Dams Ramos, et al., The effects of hypertension on the cerebral circulation. Am J Physiol Heart Circ Physiol, 2013. 304(12): p. H1598-614.10.1152/ajpheart.00490.2012.
16. Sierra, C., A. Coca, et al., Vascular mechanisms in the pathogenesis of stroke. Curr Hypertens Rep, 2011. 13(3): p. 200-7.10.1007/s11906-011-0195-x.
17. Guan, J., L. Bennet, et al., Insulin-like growth factor-1 and post-ischemic brain injury. Prog Neurobiol, 2003. 70(6): p. 443-62.
18. Feigin, V.L., M.H. Forouzanfar, et al., Global and regional burden of stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. Lancet, 2014. 383(9913): p. 245-

54.10.1016/s0140-6736(13)61953-4.

19. Rost, N.S., A. Bottle, et al., Stroke Severity Is a Crucial Predictor of Outcome: An International Prospective Validation Study. J Am Heart Assoc, 2016. 5(1).10.1161/jaha.115.002433.
20. Schwab, S., M. Spranger, et al., Plasma insulin-like growth factor I and IGF binding protein 3 levels in patients with acute cerebral ischemic injury. Stroke, 1997. 28(9): p. 1744-8.10.1161/01.str.28.9.1744.
21. Aberg, D., K. Jood, et al., Serum IGF-I levels correlate to improvement of functional outcome after ischemic stroke. J Clin Endocrinol Metab, 2011. 96(7): p. E1055-64.10.1210/jc.2010-2802.
22. Dong, X., G. Chang, et al., The relationship between serum insulin-like growth factor I levels and ischemic stroke risk. PLoS One, 2014. 9(4): p. e94845.10.1371/journal.pone.0094845.
23. Guan, J., P. Gluckman, et al., Cyclic glycine-proline regulates IGF-1 homeostasis by altering the binding of IGFBP-3 to IGF-1. Sci Rep, 2014. 4: p. 4388.10.1038/srep04388.
24. Renner, O., A. Tsimpas, et al., Time- and cell type-specific induction of platelet-derived growth factor receptor-beta during cerebral ischemia. Brain Res Mol Brain Res, 2003. 113(1-2): p. 44-51.
25. Guan, J., S. Mathai, et al., Peripheral administration of a novel diketopiperazine, NNZ 2591, prevents brain injury and improves somatosensory-motor funcion following hypoxia-ischemia in adult rats. Neuropharmacology, 2007. 53: p. 749-762.
26. Fan, D., Y. Alamri, et al., 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, 2018. 10(6).10.3390/nu10060714.
27. Zhang, R., T. Kadar, et al., - Age-related memory decline is associated with vascular and microglial. Behav Brain Res, 2012. 235(2): p. 210-7.
28. Lim, S.L., Q. Gao, et al., Vascular Health Indices and Cognitive Domain Function: Singapore Longitudinal Ageing Studies. J Alzheimers Dis, 2016. 50(1): p. 27-40.10.3233/jad-150516.
29. Raz, N., K.M. Rodrigue, et al., Vascular health and longitudinal changes in brain and cognition in middle-aged and older adults. Neuropsychology, 2007. 21(2): p. 149-57.10.1037/0894-4105.21.2.149.
30. Badran, A., M.J. Hollocks, et al., Framingham vascular age is associated with worse cognitive performance in the middle-aged and elderly. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn, 2019. 26(4): p. 531-540.10.1080/13825585.2018.1499866.
31. Lopez-Lopez, C., D. LeRoith, et al., Insulin-like growth factor I is required for vessel remodeling in the adult brain. Proc Natl Acad Sci U S A, 2004. 101(26): p. 9833-8.

32. Aleman, A. and I. Torres-Aleman, Circulating insulin-like growth factor I and cognitive function: neuromodulation throughout the lifespan. Prog Neurobiol, 2009. 89(3): p. 256-65.10.1016/j.pneurobio.2009.07.008.
33. Muller, A.P., A.M. Fernandez, et al., Reduced brain insulin-like growth factor I function during aging. Mol Cell Neurosci, 2012. 49(1): p. 9-12.10.1016/j.mcn.2011.07.008.
34. Okereke, O., J.H. Kang, et al., Plasma IGF-I levels and cognitive performance in older women. Neurobiol Aging, 2007. 28(1): p. 135-42.10.1016/j.neurobiolaging.2005.10.012.
35. Okereke, O.I., J.H. Kang, et al., Midlife plasma insulin-like growth factor I and cognitive function in older men. J Clin Endocrinol Metab, 2006. 91(11): p. 4306-12.10.1210/jc.2006-1325.
36. Fan, D., T. Pitcher, et al., Changes of plasma cGP/IGF-1 molar ratio with age is associated with cognitive status of Parkinson disease. Alzheimers Dement (Amst), 2020. 12(1): p. e12025.10.1002/dad2.12025.
37. Wang, A., Plasma cyclic Glycine-Proline/insulin-like growth factor-1 molar ratio is associated with cognitive function in elder people., in Pharmacology and Clinical Pharmacology. 2019, University of Auckland.
38. Guan, J., D. Pavlovic, et al., Vascular Degeneration in Parkinson's Disease. Brain Pathol, 2012. 16(10): p. 1750-3639.
39. Yang, P., D. Pavlovic, et al., String Vessel Formation is Increased in the Brain of Parkinson Disease. J Parkinsons Dis, 2015. 5(4): p. 821-36.10.3233/jpd-140454.
40. Yang, P., H. Waldvogel, et al., Vascular Remodelling is Impaired in Parkinson Disease. 2017. 7: p. 1-10.
41. Reid, W.G., M.A. Hely, et al., Dementia in Parkinson's disease: a 20-year neuropsychological study (Sydney Multicentre Study). J Neurol Neurosurg Psychiatry, 2011. 82(9): p. 1033-7.10.1136/jnnp.2010.232678.
42. Wood, K.-L., D.J. Myall, et al., Different PD-MCI criteria and risk of dementia in Parkinson's disease: Four year longitudinal study. npj Parkinson's Disease, 2016. 2: p. 15027.10.1038/npjparkd.2015.27.
43. Hoogland, J., J.A. Boel, et al., Mild cognitive impairment as a risk factor for Parkinson's disease dementia. Mov Disord, 2017. 32(7): p. 1056-1065.10.1002/mds.27002.
44. Pellecchia, M.T., G. Santangelo, et al., Insulin-like growth factor-1 predicts cognitive functions at 2-year follow-up in early, drug-naive Parkinson's disease. Eur J Neurol, 2014. 21(5): p. 802-7.10.1111/ene.12137.
45. Sonntag, W.E., M. Ramsey, et al., Growth hormone and insulin-like growth factor-1 (IGF-1) and their influence on cognitive aging. Ageing Res Rev, 2005. 4(2): p. 195-212.

46. Dore, S., S. Kar, et al., Distribution and levels of [125I]IGF-I, [125I]IGF-II and [125I]insulin receptor binding sites in the hippocampus of aged memory-unimpaired and -impaired rats. Neuroscience, 1997. 80(4): p. 1033-40.

47. Picillo, M., R. Erro, et al., Insulin-like growth factor-1 and progression of motor symptoms in early, drug-naïve Parkinson's disease. J Neurol, 2013. 260(7): p. 1724-30.10.1007/s00415-013-6851-0.

48. Godau, J., K. Knauel, et al., Serum insulinlike growth factor 1 as possible marker for risk and early diagnosis of Parkinson disease. Arch Neurol, 2011. 68(7): p. 925-31.10.1001/archneurol.2011.129.

49. Godau, J., M. Herfurth, et al., Increased serum insulin-like growth factor 1 in early idiopathic Parkinson's disease. J Neurol Neurosurg Psychiatry, 2010. 81(5): p. 536-8.10.1136/jnnp.2009.175752.

50. Cortes-Canteli, M. and C. Iadecola, Alzheimer's Disease and Vascular Aging: JACC Focus Seminar. J Am Coll Cardiol, 2020. 75(8): p. 942-951.10.1016/j.jacc.2019.10.062.

51. Carro, E. and I. Torres-Aleman, Serum insulin-like growth factor I in brain function. Keio J Med, 2006. 55(2): p. 59-63.10.2302/kjm.55.59.

52. Gluckman, P.D., N. Klempt, et al., A role for IGF-1 in the rescue of CNS neurons following hypoxic- ischemic injury. Biochem Biophys Res Commun, 1992. 182(2): p. 593-599.

53. Kang, D., H. Waldvogel, et al., The autocrine regulation of insulin-like growth factor-1 in human brain of Alzheimer’s disease. Psychoneuroendocrinology, 2021. 127: p. 105191.

54. Procter, T.V., A. Williams, et al., Interplay between Brain Pericytes and Endothelial Cells in Dementia. Am J Pathol, 2021. 191(11): p. 1917-1931.10.1016/j.ajpath.2021.07.003.

55. Di Marco, L.Y., A. Venneri, et al., Vascular dysfunction in the pathogenesis of Alzheimer's disease--A review of endothelium-mediated mechanisms and ensuing vicious circles. Neurobiol Dis, 2015. 82: p. 593-606.10.1016/j.nbd.2015.08.014.

56. Watanabe, K., K. Uemura, et al., The participation of insulin-like growth factor-binding protein 3 released by astrocytes in the pathology of Alzheimer's disease. Mol Brain, 2015. 8(1): p. 82.10.1186/s13041-015-0174-2.

57. Cheng, J., B.J. North, et al., The emerging roles of protein homeostasis-governing pathways in Alzheimer's disease. Aging Cell, 2018. 17(5): p. e12801.10.1111/acel.12801.

58. Li, F., K. Liu, et al., Cyclic glycine-proline administration normalizes high-fat diet-induced synaptophysin expression in obese rats. Neuropeptides, 2019. 76: p. 101935.10.1016/j.npep.2019.05.006.

59. Singh-Mallah, G., K. Singh, et al., Maternally Administered Cyclic Glycine-Proline Increases Insulin-Like Growth Factor-1 Bioavailability and Novelty Recognition in Developing Offspring.

Endocrinology, 2016. 157(8): p. 3130-9.10.1210/en.2016-1189.

60. Singh-Mallah, G., M. Ardalan, et al., Administration of cyclic glycine-proline during infancy improves adult spatial memory, astrocyte plasticity, vascularization and GluR-1 expression in rats. Nutritional neuroscience, 2021. 25(12): p. 10.10.1080/1028415X.2021.1980845.
61. Williams, I.C., M.H. Park, et al., Cognitive Function and Vascular Risk Factors Among Older African American Adults. J Immigr Minor Health, 2018. 20(3): p. 612-618.10.1007/s10903-017-0583-7.
62. Doiron, M., M. Langlois, et al., The influence of vascular risk factors on cognitive function in early Parkinson's disease. Int J Geriatr Psychiatry, 2018. 33(2): p. 288-297.10.1002/gps.4735.
63. Lo Coco, D., G. Lopez, et al., Cognitive impairment and stroke in elderly patients. Vasc Health Risk Manag, 2016. 12: p. 105-16.10.2147/vhrm.S75306.
64. Picillo, M., R. Pivonello, et al., Serum IGF-1 is associated with cognitive functions in early, drug-naive Parkinson's disease. PLoS One, 2017. 12(10): p. e0186508.10.1371/journal.pone.0186508.
65. Wennberg, A.M.V., C.E. Hagen, et al., The association between peripheral total IGF-1, IGFBP-3, and IGF-1/IGFBP-3 and functional and cognitive outcomes in the Mayo Clinic Study of Aging. Neurobiol Aging, 2018. 66: p. 68-74.10.1016/j.neurobiolaging.2017.11.017.