



Review Article

Parkinson's Disease and Type-2 Diabetes: Methylglyoxal may be a Common Causal Agent; Carnosine could be Protective

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Abstract

The likelihood that the type-2 diabetes influences the incidence of Parkinson's disease (PD), via increased generation of methylglyoxal (MG), is examined in the light of recent evidence. Animal experiments (mice and dogs) have shown that high glycemic index diets increase tissue MG levels, while low glycemic index diets in humans are associated with a decreased incidence of PD. Proteomic studies have revealed an increased activity of the carnosinase, CNBP2, in the substantia nigra of PD patients. It is therefore suggested that carnosine could, by reacting with MG and by interfering with glycolysis, exert protection against PD onset. Carnosine's potential efficacy towards diabetic-related hyperalgesia is also discussed.

Keywords: Parkinson's disease; Methylglyoxal; Glycolysis; Triose phosphates; Dopamine; Glycation; Neuropathy; Hyperalgesia; Carnosinase

Introduction

It is generally accepted that there is a relationship between T2D and Alzheimer's disease (AD) [1-5] and cognitive decline [6,7], and that methylglyoxal (MG) may be a common causative agent [8]. MG is formed mostly via the spontaneous decomposition of two glycolytic intermediates, the triose phosphates glyceraldehyde-3-phosphate and dihydroxyacetone phosphate, other sources include amino acid catabolism and lipid catabolism. There is considerable literature showing MG toxicity; it readily reacts with arginine, lysine and histidine residues in proteins and is a major cause of protein carbonyl formation and their subsequent cross-linking to unmodified polypeptides [9,10]. Much pathology associated with T2D derives from MG-mediated protein damage. Furthermore MG can compromise intracellular proteolysis [11] and damage mitochondria and DNA [12,13], mimicking many of the effects of aging; indeed it has been proposed that dietary restriction-induced lifespan extension is mediated, at least in part, by lowered MG formation [14,15]. It has also been suggested that increased formation of advanced glycation end-products (AGEs), possibly via raised MG levels, is a likely route of age-related dysfunction [10,16,17].

It has also been recently shown [18] that feeding mice with 20%

sucrose-sweetened water for 7 months induced (in their brains) not only metabolic alterations typical of T2D (such as oxidative dysfunction) but also increased amyloid- β levels, a major AD hallmark. Possible explanations include increased MG formation (via glycolysis and/or the polyol pathways) and compromised amyloid- β elimination due to sugar-induced hyperinsulinemia coupled with the fact that amyloid- β and insulin compete for the same protease (IDE or insulin-degrading enzyme) for clearance, and that the amyloid- β peptide can provoke mitochondrial dysfunction [19]. These findings clearly illustrate the probably relationship between diet and AD and T2D and point to the likelihood that these age-related pathologies not only have common aetiologies but also may interact synergistically and deleteriously [20]. It has also recently been shown that MG can induce Tau hyperphosphorylation, another prominent molecular hallmark of AD [21].

A number of recent papers have indicated that there may also be a relationship between Parkinson's disease (PD) and T2D [22-24]. It is suggested here that (i) a common underlying causal mechanism linking PD to T2D involves increased levels of MG and (ii) the naturally-occurring dipeptide carnosine (β -alanyl-L-histidine) may be potentially ameliorative to PD pathology.

Parkinson's disease and diet

Whilst there are recognized genetic causes of PD, the majority of cases are seemingly spontaneous in origin and the possibility of a dietary influence cannot therefore be excluded. For example, in 2010 a paper from Japan [25] suggested that PD risk was related to dietary constituents. More recently, two other papers have also pointed to an association between diet and PD; adherence to a Mediterranean diet was associated with a low incidence of PD [26], and diets rich in vegetables, fruit and fish in Japanese subjects was associated with a decreased risk of PD [27]. Ketogenic diets, which are low glycemic index, have been shown to exert protective activity towards various aspects of PD pathology, for example MPTP toxicity [28] and 6-hydroxydopamine toxicity [29]. Indeed it has been proposed that ketogenic diets may have therapeutic potential for a number of neurological disorders [30].

As noted above, T2D is generally associated with excessive chronic glucose metabolism, and many of the pathological consequences appear to be driven by formation of macromolecular modifications (mostly to proteins) called advanced glycation end-products (AGEs), mediated primarily by MG.

Recent animal studies (in mice and dogs) have shown that sera levels of MG can be significantly lowered by employing low glycemic index diets [11,31]. For example after only one hour following consumption of a high glycemic index diet, the MG levels in dog sera were increased by 40% compared to animals fed the low glycemic index diet [31]. It appears that the high glycemic index diet promoted a higher rate of glucose catabolism which induced increased MG formation, either via the normal glycolytic route or via the polyol pathway, both of which raise levels of triose phosphates from which MG spontaneously forms. In contrast, the low glycemic index diet was associated with lower sera MG levels. The study

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in mice showed that high glycemic index diets (similar to typical North American diets) can profoundly influence MG generation in a number of tissues, including liver, retina, lens and the brain [11] (Table 1). Notably in these experiments it was found that the brains of animals fed a high glycemic index diet contained a huge, 34-fold, increase in MG-modified proteins, primarily in the substantia nigra, compared to animals fed a low glycemic index diet [11]. Although the dietary induced increase in MG in the substantia nigra has yet to be confirmed by others, it is reasonable to conjecture that high glycemic index diets in humans could also raise tissue MG levels in human brains and retinas.

Methylglyoxal and dopamine

Not only does MG react readily with proteins, amino lipids and DNA, but it was shown almost 40 years ago that MG can react with dopamine [32] to generate a product which was possibly toxic. Very recently this product has been characterized and shown to be a salsolinol-like compound, 1-acetyl-6,7,-dihydroxy-1,2,3,4-tetrahydroisoquinoline (ADTIQ) [33] whose structure strongly resembles that of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), a well-known cause of experimentally-induced mitochondrial dysfunction characteristic of PD. Importantly, ADTIQ was also found to accumulate in PD brains [33]. The proposed reaction of MG with dopamine therefore provides an additional causative route of PD pathology.

Methylglyoxal and Parkinson's disease proteotoxicity

PD is strongly associated with the accumulation and aggregation of α -synuclein [34]. Furthermore α -synuclein is highly susceptible to glycation, while α -synuclein "knockout" mice exhibit increased levels of MG, glycation stress and glyoxalase activity [35]. Not only can MG induce protein glycation and formation of protein-AGEs but it can also stimulate transglutaminase activity, at least in porcine tenocytes [36]. Increased tissue transglutaminase activity is another characteristic of PD and α -synuclein may be a substrate for transglutaminase in PD [37]. Thus it is conceivable that MG could stimulate transglutaminase-mediated α -synuclein cross-linking and thereby contribute to Lewy body formation.

Proteasomal dysfunction has also been recognized as part of the PD pathology [38,39]. There is recent evidence showing that dietary-induced raised tissue levels of MG can substantially interfere with the ubiquitin-proteasomal apparatus which is normally responsible for the selective elimination of aberrantly modified polypeptide chains. Uchiki et al. demonstrated that in the high glycemic index diet mice, not only were the glycated protein substantially resistant to proteasomal-mediated proteolysis, but ubiquitin itself was also glycated by MG, which compromised its participation in ubiquitin-proteasomal-mediated proteolysis [11].

Table 1: The effects of dietary glycemic index (GI) on relative levels of methylglyoxal-induced protein AGE, i.e. hydroimidazolone adducts (MG-H1), in mouse tissues. NB Values are expressed relative to those observed in the appropriate tissue of the animals fed the low GI diet [11].

Diet for 10 months	Relative levels of MG-H1 (approximate)			
	Retina	Liver	Lens	Brain (substantia nigra)
High GI	3	7	8	34
Low GI	1	1	1	1

Parkinson's disease genetics and methylglyoxal

Recent genetic evidence supports the proposition that MG plays a causal role in PD. There are a number of genetic defects which increase the risk of PD in humans. Amongst these is the DJ-1 gene, a defect in which can cause early-onset PD. DJ-1 controls the level the nuclear transcription factor E2-related factor (Nfr2) [40], which in turn upregulates the cellular response to oxidative stress, including the MG detoxifying enzyme glyoxalase-1 [41]. Furthermore, a recent study has shown that the purified DJ-1 gene-product is a novel form of glyoxalase [42].

Evidence suggesting that PD may be associated with over-activation of glycolysis and decreased mitochondrial function has recently been obtained from a study in *Drosophila* [43]. Defects in the gene *Parkin* are associated with early onset PD; when the defective gene was introduced into *Drosophila* larvae, decreased locomotion was observed, due to lowered ATP levels resulting from compromised respiration, but glycolysis was in fact upregulated. Additionally, a cell-based study has revealed that the *Parkin* gene product, Parkin, regulates energy metabolism [44]: over-expression of Parkin was found to decrease glucose uptake, decrease glycolytic rate and stimulate oxygen consumption, whereas Parkin deficiency decreased expression of certain mitochondrial genes, but enhanced glucose uptake and glycolytic rate [45]. As noted above, one consequence of excessive glycolysis is the production of MG. MG will also be produced if triosephosphates accumulate due, for example, to decreased NAD⁺ availability or compromised glyceraldehyde-3-phosphate dehydrogenase activity. It is interesting to note that PD is associated with (i) mitochondrial dysfunction which may prevent NADH oxidation back to NAD⁺ (via the malate or glycerol-phosphate shuttles) and (ii) increased oxidative damage to glyceraldehyde-3-phosphate dehydrogenase in the cerebral cortex [46]. These observations are at least consistent with the view that increased or excessive glycolysis may contribute to the development of the PD phenotype via generation of MG in amounts which exceed cellular ability in the substantia nigra to deal with it.

A recent paper reported the over-expression of CNBP2 in the substantia nigra of PD patients; CNBP2 protein levels were found to be increased between 2½ and 3-fold compared to control subjects [47]. CNBP2 is a non-specific carnosinase usually located in the cellular cytosol. An age-related increase in another carnosinase (presumably CNBP1) expression in the substantia nigra has been previously noted [48]. Consequently the presence of raised levels a carnosinase activities in the substantia nigra of PD subjects can be interpreted (but other interpretations are also possible) to suggest that (i) carnosine (β -alanyl-L-histidine) is somehow protective towards the development of PD, and (ii) elevated levels of carnosinase in the PD patients increases carnosine destruction in the substantia nigra, thereby increasing the likelihood of PD pathology.

Carnosine and Parkinson's disease

Carnosine, although previously described as enigmatic and forgotten [49], is synthesized in the brain in glia and oligodendrocytes [50] and is degraded back to its component amino acids by two carnosinases, CNBP1 and CNBP2. Carnosine is a common component of carnivorous diets being present in muscle and brain of most mammals [51], sometimes at very high concentrations (e.g. 100mM in trained racehorse muscle) [52]. Fish muscle also frequently

contains high levels of carnosine and/or related peptides such as anserine and balenine [53].

There is preliminary evidence to support the idea that carnosine possesses therapeutic potential towards PD [54-56]. Scattered amongst the literature are a number of papers suggesting that carnosine may ameliorate certain aspects of PD pathology (Table 2). These include effects on α -synuclein polymerization [57-59], metal ion chelation [60] and toxicity suppression of [61-65]. Additionally carnosine has been shown to stimulate vimentin expression in cultured fibroblasts [66]. It is possible that vimentin is involved in formation of (protective?) aggresomes into which toxic protein aggregates, such as α -synuclein, may be sequestered [67]. Whether carnosine upregulates vimentin expression in neuronal tissue is unknown however.

In model systems carnosine has been shown to protect proteins against MG-mediated modifications [68,69], protect bacteria against high glucose-induced stress [70], suppress glucose-induced secondary complications in diabetic mice [71], protect cultured neurones against amyloid peptide toxicity [72,73], and suppress Alzheimer's disease pathology in transgenic mice [74].

It is possible that the presence of carnosine may, by scavenging MG, prevent the generation of ADTIQ from dopamine (described above). Indeed it has been shown that carnosine can suppress ADTIQ toxicity [75] possibly by either quenching ROS and RNS or inhibiting ROS generation. Additionally, whether carnosine can actually compete with dopamine to form a carnosine-MG adduct, thereby preventing ADTIQ generation, is unknown at present, but is certainly worthy of investigation.

If carnosine is generally protective towards neurodegenerative conditions, the above-mentioned age-related increase in carnosinase expression may also help to explain why so many neurological pathologies are age-related. It is known that the carnosine content of

human muscle decreases in old age [76], but to the author's knowledge nothing is known about carnosine levels in human substantia nigra.

Carnosine may also be protective towards human diabetic kidney disease where an inverse relationship has been observed between normal kidney function and tissue carnosinase activity [77]. Given that MG is thought to be responsible for much diabetic nephropathy, this again indicates the possibility that increased carnosine levels may contribute to the suppression of MG-mediated pathology. However it should be pointed out that the mechanism by which carnosine protects the kidney against bicarbonyl toxicity remains to be established. Nevertheless, the observations that pathology is enhanced when carnosinase activity is raised in both kidney and substantia nigra is consistent with the proposal that carnosine may exert some protective function towards MG-mediated molecular modification.

Carnosine and glycolysis

The above discussion of the likely relationship between diet and PD has emphasized the role that elevated glycolytic flux rates may play in increasing the potential for MG generation. It is also possible that carnosine may partially inhibit MG formation by interfering with glycolysis. Studies in cultured tumour cells and in yeast have produced evidence showing that carnosine may inhibit glycolytic flux to some extent. A study in cultured glioma tumor cells showed that addition of carnosine inhibited growth by lowering glycolytically-synthesized ATP levels [78], although the exact mechanism responsible have yet to be determined. In yeast it was shown that carnosine induced up to 20% cell death in cells cultured solely on glucose as carbon source (i.e. during anaerobic fermentation); however, no deleterious effects were observed in yeast cells growing aerobically on glycerol [79]. Again the mechanism underlying these effects has not been determined. However, it was found more than 25 years ago that carnosine stimulates the activity of the gluconeogenic enzyme fructose-1,6-bisphosphatase (FBPase) [80]. If such a stimulation also occurs *in vivo* then this would create an ATP-consuming futile cycle which would substantially lower intracellular ATP levels and the production of triose phosphates (and hence MG) as well as other metabolic intermediates required for growth in cells utilising glucose as sole carbon source. It is relevant to note that FBPase has recently been found to possess regulatory activity towards energy metabolism, including effects upon G3P and DHAP (i.e. MG precursors) levels [81]. Moreover, FBPase gene transcription is induced by the PGC-1 α [82], an important transcription factor regulating energy metabolism; i.e. PGC-1 α stimulates mitogenesis and mitochondrial activity and suppresses glycolysis, as is observed during caloric restriction-mediated lifespan extension. Hence one can suggest that, in addition to any MG-scavenging action, carnosine may behave as a caloric restriction mimetic by exerting suppressive effects on glucose metabolism by acting directly on FBPase (and downstream of PGC-1 α transcriptional control) which would nevertheless decrease the potential for MG formation. In fact carnosine has been shown to exert anti-senescent activity in cultured human fibroblasts [83], senescence accelerated mice [84] and fruit flies [85], observations consistent with the proposal that carnosine may mimic some aspects of caloric restriction.

Zinc, carnosine and Parkinson's disease

A recent paper has demonstrated possible a link between zinc ion accumulation in a PD model and accumulation of dihydroxyacetone-

Table 2: Preliminary evidence and hypothetical routes by which carnosine could ameliorate intracellular changes associated with Parkinson's disease.

Some factors suggesting a therapeutic role for carnosine in PD	Reference
Carnosine supplementation beneficial to PD patients	Boldyrev et al. [54,55]
Carnosinase (CNDP2) over-expressed in PD substantia nigra	Licker et al. [47]
Carnosine could:	
(a) Suppress MG formation by inhibiting glycolysis	Renner et al. [78] Cartwright et al. [79]
(b) Maintain/stimulate mitochondrial activity	Cartwright et al. [79]
(c) Quench ROS activity	Kohen et al. [97] Quinn et al. [98]
(d) Suppress MG-induced protein damage	Hipkiss and Chana [68] Brownson and Hipkiss [69]
(e) Suppress MG reaction with dopamine; decrease ADTOQ formation	Deng et al. [33]
(f) Suppress ADTOQ activity	Kang [75]
(g) Inhibit α -synuclein polymerization	Kang and Kim [57]
(h) Chelate toxic metal ions (e.g. zinc)	Tromblay et al. [60]
(i) Stimulate vimentin expression and aggresome formation.	Ikeda et al. [66]

MG: Methylglyoxal; ROS: Reactive oxygen species; ADTIQ: 1-acetyl-6,7,-dihydroxy-1,2,3,4-tetrahydroisoquinolin

phosphate (DHAP) in near pure cultured cortical neurones obtained from mice [86]. However, the exact relationship between DHAP accumulation and zinc release is unclear (i.e. which, if either, is the causal event?); furthermore not only is DHAP an effective glycation agent but it spontaneously decomposes into MG. This paper also demonstrated the ameliorating effect of a zinc ion chelator [87]. As carnosine is also a zinc chelator [88], it is suggested that the dipeptide should also be investigated in this model system with regard to amelioration of zinc toxicity, DHAP formation and protein glycation.

Methylglyoxal, metabolic neuropathy, hyperalgesia and carnosine

Two recent papers [87,88] clearly illuminate the role that MG plays in diabetes-related hyperalgesia and associated metabolic neuropathies. Possible ameliorative strategies included aminoguanidine (AG) which was able to suppress the MG-induced hyperalgesic effects. Although AG is a well-recognized carbonyl scavenger, it is also toxic and has consequently been withdrawn from clinical trials. The MG scavenging activity of a synthetic peptide, GERP₁₀, was also found to protect the neuronal Nav1.8 site against MG [87], thereby demonstrating the efficacy of the idea that diverting the MG extracellularly to another location was sufficient to provide protection. However it is unlikely that oral administered GERP₁₀ would survive enzymatic destruction in the digestive tract. However, carnosine, which is virtually non-toxic and is not hydrolysed by digestive peptidases, can suppress hyperalgesia as it exerts anti-nociceptive actions in diabetic mice [89,90]. On the assumption that carnosine similarly exerts anti-nociceptive activity in humans, it is suggested that diabetic diets enriched in carnosine, either added as a supplement or using carnosine-rich foods such as certain meats and fishes, should be explored. This may not only decrease much diabetes related pathology but also suppress hyperalgesia as a consequence of carnosine reacting with MG and there preventing MG-induced modification of the neuronal voltage-gated sodium channels.

Carnosine administration

The presence of serum carnosinase activity is frequently regarded as an impediment to dietary-mediated carnosine therapy. However it is possibly relevant to note that the olfactory lobe is normally enriched in carnosine [91] and an early symptom of PD is loss of sense of smell [92]. In order to circumvent the carnosinase problem one solution could be to use intranasal delivery [93,94] as carnosine can cross the blood brain barrier. It is unknown whether carnosine levels in the olfactory lobe change with age or in PD, however the author has received an anecdotal report that orally administered carnosine can improve/restore senses of smell and/or taste in some human patients. Another approach is to employ D-carnosine which is not cleaved by serum or cytosolic carnosinases, but its uptake into the tissues may be slower than L-carnosine [95].

Conclusions

Recent research supports the proposition that sugar stress [96], via the increased formation of MG, is important to PD-associated pathology and which is in agreement with other proposals concerning the possible association between T2D and PD. Epidemiological evidence has shown that dietary glycemic index may play a role in controlling PD incidence, while animal experiments have demonstrated that tissue MG levels are strongly influenced by dietary glycemic index. It is possible that carnosine,

a naturally-occurring and essentially non-toxic peptide, may exert some protection against MG-induced dysfunction (see table 2 for summary of hypothetical mechanisms). It is suggested that factors which influence tissue carnosine levels, such as diet and endogenous carnosinase activity, could also affect PD onset. Carnosine's positive effects towards diabetic complications and AD-associated pathology in animal and model studies are indicative of its potential therapeutic utility, especially in a form which resists carnosinase attack. It is therefore suggested that the therapeutic potential of carnosine and related peptides, together with strategies which suppress carnosinase expression or activity, should be further explored with respect to PD.

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