Energy metabolism and autism: the ameliorative potential of carnosine and agmatine

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Abstract

Recent studies have revealed that autistic spectrum disorders (ASD) is associated with enhanced glycolysis (i.e. establishment of the Warburg effect) accompanied by increased formation of glycated proteins in sera and urine. It is thought that, in the brain, originating in the gut tissue or more likely in the microbiome (mostly Clostridia bacterial species) [14]. It is thought that, in the brain, mitochondrial dysfunction [7-10], and a three-fold decline in oxidative phosphorylation has been detected in ASD subjects’ granulocytes [10]. It would obviously be informative to determine if this deficit is systemic and also occurring in the CNS or exhibited solely in granulocytes.

Introduction

A recent publication has suggested that autism spectrum disorders (ASD) is accompanied, associated and/or related to changes in energy metabolism, more specifically the imposition of enhanced aerobic glycolysis, coupled with a suppression of mitochondrial ATP synthesis, also known as the Warburg effect [1]. Another recent paper has revealed the presence of elevated amounts of oxidized, nitrated and glycated proteins in the plasma of some ASD subjects, as well as a disturbance in arginine metabolism and/or clearance [2]. The objective of the present piece is to attempt to integrate these findings by highlighting the possible ameliorative roles of carnosine and agmatine (decarboxylated arginine), both of which are diminished in sera of some ASD subjects [3-5].

Energy metabolism and ASD

The Vallée and Vallée hypothesis [1] proposes that ASD is strongly associated with “a shift in energy production from mitochondrial oxidative phosphorylation to aerobic glycolysis – despite the availability of oxygen” i.e. the imposition of the Warburg effect. Plausible mechanistic routes proposed include the WNT/beta-catenin pathway, and activation of the regulatory complex PI3Akt/mTOR [1].

It is uncertain whether the induction of the predominantly glycolytic metabolism is caused primarily by dysfunction of the PI3Akt/mTOR regulatory complex, provoked perhaps by glycated protein (also called advanced glycation end-products i.e. AGEs) [6] or whether the imposition of the Warburg-type metabolism is a response to some other causative event or events, such as mitochondrial dysfunction. Indeed, it has been claimed that ASD is associated with mitochondrial dysfunction [7-10], and a three-fold decline in oxidative phosphorylation has been detected in ASD subjects’ granulocytes [10]. It would obviously be informative to determine if this deficit is systemic and also occurring in the CNS or exhibited solely in granulocytes.

There is evidence suggesting that formation and/or accumulation of propionic acid is associated with some cases of ASD [11-13], possibly originating in the gut tissue or more likely in the microbiome (mostly Clostridia bacterial species) [14]. It is thought that, in the brain,

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compound, methylglyoxal (MG), produced following spontaneous decomposition of the glycolytic intermediates, dihydroxyacetone-phosphate and glyceraldehyde-3-phosphate. MG is a strong glycatin agent and well-recognised as a major source of the post-synthetic protein modifications which characterise both type-2 diabetes and ageing [21,22]. The notion that ASD is associated with enhanced MG generation is supported by the detection in some autistic subjects of gene polymorphisms in the MG detoxification enzyme, glyoxalase-1 [23-26], which could result in decreased MG elimination and increased macromolecular glycation. The increased glycolytic activity could therefore account for the raised levels of glycated proteins detected in autistic patients’ plasma and urine [2], especially if glyoxalase-1 activity was insufficient to meet the increased generation of MG. However, it must be pointed out that the suggestion that ASD is associated with glyoxalase dysfunction has been disputed [27,28]. Never-the-less, it is interesting that (i) changes in glyoxalase-1 expression in white blood cells seems to influence mood in human subjects [29], and (ii) it has recently been reported that erythrocytes of autistic boys possess lower levels of the detoxification enzyme retinal dehydrogenase (RALDH1), than was present in controls [30], observations which suggest that detoxification deficiency may influence behaviour in ASD individuals. The possibility that autism is associated with aldehyde toxicity generally and acetaldehyde in particular, has been proposed [31]. Furthermore, it has recently been shown that MG readily reacts with β-alanine [32], a reaction which would decrease pantothenate synthesis and further compromise formation of the CoA in the microbiome, as outlined above. Additionally the microbiome can also generate a well-studied neurotoxin, 3-nitropropionic acid (3NPA), presumably from propionic acid, which can induce a range of neuropathologies in model animals [33], although no specific claims for ASD have been made. Biochemically, 3NPA inhibits the TCA cycle enzyme succinate dehydrogenase, thereby compromising mitochondrial ATP synthesis and so could induce a Warburg-like metabolic state. It is likely that any gut organism in which propionic acid accumulates (as discussed above) may also increase the potential for 3NPA generation following attack by reactive nitrogen species (RNS); it is noteworthy ASD sera is enriched with nitrated proteins [2]. Consequently, it is possible to integrate a number of observations associated with ASD, including mitochondrial dysfunction, propionic acid accumulation, increased urinary β-alanine levels, decreased pantothenate levels, decreased glyoxalase-1 activity, and raised levels of sera oxidised, nitrated and glycated proteins.

There are additional evidence that ASD may be associated directly with changes in energy metabolism. A number of studies showing that the anti-aging agent ramapycin, which suppresses mTOR signalling activity to decrease glycolysis and upregulate oxidative phosphorylation, also suppresses autism-like behaviour in animal models [34,35]. Glycated proteins (AGEs) have been shown to activate mTOR [6] and elevated mTOR activity was detected in cells obtained from ASD children [36,37], suggesting a possible causative relationship between these phenomena. Animals exposed to valproic acid have been used as an animal model of ASD [38]: amongst the resultant effects of valproic acid is a dose dependent stimulation of glycolysis [39] and, perhaps even more importantly, it has previously been observed that resveratrol, an anti-diabetic agent which inhibits non-enzymic glycosylation (glycation) of proteins [40], prevents valproic acid-induced social impairment in these animals [41]. Furthermore, ketogenic diets (presumably provoking very little glycolysis) have been shown to be somewhat effective in controlling ASD behavioural symptoms in human subjects [42]. Although it is uncertain whether these effects are mediated via the microbiome or specifically in the cells of CNS, these findings are nevertheless consistent with the suggestion that ASD is associated with increased protein glycation resulting from enhanced glycolysis and MG generation.

Deficiency in vitamin-D has also been proposed to play a role in ASD [43-45] and it has been claimed that vitamin D supplementation in children may improve symptoms of ASD [46]. It is interesting to note that vitamin D appears to play a role in controlling the reaction between advanced glycation end-products (AGEs) with their cellular receptors (RAGEs) [47-49], again observations consistent with the findings of elevated levels of protein glycation in ASD subjects.

**Carnosine and ASD**

The dipeptide carnosine (β-alanyl-L-histidine), when given as a dietary supplement to autistic children, has been shown to exert beneficial effects on behaviour [50,51]. Furthermore, the levels of carnosine in urine [52] and sera [53] of autistic subjects are reported to be substantially lower (by up to 75%) than in controls.

Although first described more than 100 years ago [54], carnosine was regarded as "enigmatic" [55]; its precise physiological function still remains uncertain. Amongst the variety of suggestions, all supported with evidence using model and/or cell and animal studies, carnosine can behave as a hydrogen ion buffer, anti-oxidant, anti-glycator, wound-healing agent, metal ion chelator, whilst beneficial effects towards diabetes, atherosclerosis, heart failure, tumour cell growth and cellular ageing have also been reported [56-58]. Interestingly, dietary supplementation studies in human subjects have revealed improvement in cognition and/or behaviour in schizophrenics [59], elderly subjects [60], Gulf War veterans [61] and as well as autistic children [3,53].

There are a number of possible mechanisms by which carnosine might ameliorate aspects of ASD. First, the additional presence of dietary dipeptide carnosine could, following its hydrolysis, provide a supply of β-alanine and thus allow pantothenate and CoA synthesis in the microbiome, and thereby permit effective oxidative phosphorylation and perhaps additionally ensuring removal of the propionic acid via its carboxylation using acetyl-CoA kinase. Secondly, as outlined above, in order to maintain ATP levels, a compensating response to mitochondrial dysfunction would be enhanced glycolysis, despite the presence of oxygen (i.e. Warburg effect). There is evidence that carnosine can partially suppress glycolysis and decrease glycolytic ATP synthesis in yeast [62] and in transformed cells [63-65], which may decrease synthesis of triose phosphates and MG formation. Carnosine can also directly react with methylglyoxal [66] and other reactive carbonyl compounds [67], as well as inhibit formation of glycated proteins as shown in whole animal studies [68,69] and in humans [70]. Carnosine has also been shown to exert regulatory effects on mitochondrial function [71,72] as well as activate the Nrf2 transcription factor (regulator of the antioxidant response) and thereby enhance oxidative defence [73,74]. It is relevant to note that autism in young boys is associated with alteration in Nrf2 expression and/or function [75,76]. Furthermore, it should be noted that carnosine may mimic ramapycin to some degree in its ability to inhibit mTOR activity [77]; as noted above, ramapycin is a well-recognised mTOR inhibitor that exerts beneficial effects towards ASD subjects and in animal models [35,36,78].

These properties (inhibitory effects on mTOR and glycolysis, suppression of MG-induced macromolecular modifications and enhancement of anti-oxidant defence) exhibited by carnosine
would appear to counter the onset of the Warburg effect and might account for the beneficial effects of carnosine towards at least some aspects of ASD. Furthermore, carnosine has been shown to suppress acetaldehyde-mediated toxicity towards cultured cells [79] and DNA-protein cross-linking in a model system [66], observations consistent with the proposal that ASD is somehow associated with acetaldehyde-mediated dysfunction. It is interesting to note that carnosine seems to possess many of the properties which are likely to suppress generation of the changes exhibited by sera and urinary proteome detected in ASD subjects [2].

There is also a study showing that carnosine can ameliorate the deleterious effect of propionic acid in an animal model of ASD, although the mechanisms responsible have not been explored [80]. Recent studies have suggested that the DJ-1 protein complex can facilitate protein deglycation [32], including glycated β-alanine (induced by MG). Many years ago it was suggested that carnosine might participate the repair of glycated proteins (via deglycation and/or transglycation), perhaps acting as a recipient of the detached glycating agent [81]. However, the possibility that carnosine might participate in protein deglycation has not been explored experimentally.

Carnosine can also inhibit protein nitration by forming adducts such as NO-carnosine and carnosine nitrite [82]. Given that raised levels of protein nitration have been detected in ASD plasma and urine [2], as well as in hair and nails [83], this may partly explain carnosine’s ability to moderate aspects ASD behaviour [50].

More recently it has been shown that romidepsin can ameliorate autism-like behavioural symptoms in a mouse model of ASD [84] by binding to zinc ions in the zinc pocket of histone deacetylase and thus altering gene expression. As carnosine is a well-known zinc chelator, one wonders if the dipeptide might also bind the zinc in histone deacetylase in a manner similar to romidepsin.

**Agmatine and ASD**

There is evidence from an animal study that agmatine (decarboxylated arginine) can be beneficial towards valproic acid-induced autism-like symptoms of ASD in an animal model [85] and that some ASD subjects possess decreased levels of agmatine in their sera [5]. While there is evidence that agmatine possesses anti-inflammatory properties [86,87], there is little direct evidence of any anti-glycation activity of agmatine, although the structure of the molecule (an amino group plus the guanidino group) resembles the strong but toxic anti-glycator, aminoguanidine. Consequently, it is suggested that agmatine should be very readily glyated by a variety of reactive aldehydes, including MG and acetaldehyde, although this property does not appear to have been investigated. Never-the-less it is very relevant to note that agmatine can bind ADP-ribose [88] which may indicate agmatine’s possible inhibitory action towards protein modification by ADP-ribose, or its participation in reversible protein modification (e.g. NAD-dependent histone deacetylation or polyADP ribosylation). The fact that agmatine activity has been likened to that of the anti-aging agent rapamycin [89], including mTOR inhibition, suppression of glycolysis and activation of mitochondrial activity [90], supports this idea. The findings that ASD is associated with changes in arginine metabolism [35] and its intracellular distribution [2] reinforces the proposal that arginine’s decarboxylation product, agmatine, might be ameliorative [91].

It is perhaps also interesting to note that agmatine can promote an increase in cyclic-AMP levels in tissues [90], but cyclic-AMP has been reported to suppress carnosine synthesis [92]. Such observations might suggest that while agmatine can suppress carnosine synthesis, but upon its glycation agmatine may not suppress carnosine synthesis, which could indicate a possible regulatory mechanism of carnosine production in response to endogenous and exogenous glycating agents. Agmatine has been shown to inhibit polyamine synthesis, but whether this property is suppressed following agmatine glycation has not been investigated. However, it has been proposed that polyamines generally can, by being readily glycated themselves [93], behave protectively and thereby prevent glycation of polypeptides and nucleic acids.

**Conclusions**

ASD causation is undoubtedly complex [94]; amongst the factors so far recognised are changes in the microbiome, enhanced glycolytic activity, mitochondrial dysfunction and alteration in redox activity, all of which, presumably together with unrecognised metabolic and exogenous agents, contribute to varying degrees to the changes in behaviour and social interaction which characterise autism. Amongst these factors are agents such as AGEs which affect energy metabolism directly or indirectly, especially glycolysis, oxidative phosphorylation and their potentially dysfunctional, glycated, by-products.

The proposal that ASD is associated with mTOR activation leading to enhanced glycolytic activity as exemplified by the establishment of the Warburg effect (as proposed by Vallée & Vallée, [1]) is supported by the findings that not only is a ketogenic diet beneficial towards ASD [95], but that glycated proteins (i.e. AGEs) can indeed activate mTOR to provoke onset of the Warburg effect [6]. Thus carnosine and possibly agmatine, both being pluripotent and essentially non-toxic endogenous molecules which can decrease glycosylation, possibly via effects on mTOR [77,89], plus their reactivity towards reactive carbonyls such as MG, may inhibit protein glycation and thereby ameliorate some of the consequences of increased glycolytic activity and exert beneficial effects on aspects of behaviour in ASD children. Although the specific mechanisms by which some of these effects are mediated may differ; for example control of protein nitration may occur via carnosine’s direct reaction with the nitrating agent whereas agmatine may inhibit nitric oxide synthesis, such complementary mechanisms could conceivably be therapeutically efficacious. That changes in both carnosine and agmatine may be connected to ASD is also supported by the findings that their serum levels are substantially lower in ASD subjects and that they both can also ameliorate the effects of propionic acid, which is known to sometimes accumulate in ASD. It is also suggested that the ability of carnosine and agmatine to ameliorate the effects of MG, either directly or following upregulation of antioxidant defences may also contribute to their efficacy towards ASD. It is interesting to note that two of propionic acid’s likely metabolites, 3-nitropropionate [96] and propionaldehyde [97], have also been associated with ASD; both carnosine and agmatine, could theoretically antagonise either their formation and/or toxicity via inhibiting propionate nitration or promoting aldehyde scavenging.

Whether combined treatment with both carnosine and agmatine is therapeutic towards ASD has not been explored. However, it has been noted that co-administration of carnosine and arginine (agmatine precursor) was more effective in combating hypoxic stress in rats than when either agent was supplied singly [98], an observation at least consistent with the above suggestion. More generally, as both carnosine and agmatine [99] when administered separately seem to exert beneficial effects towards aspects of both Parkinson’s disease [71,100,101] and Alzheimer’s disease [102-104] in cellular and animal
models, then perhaps their co-administration should be also explored towards these age-related neurodegenerative conditions.

Conflicts of interest
There are no conflicts of interest.

References
1. Valicke A, Valicke JN (2018) Warburg effect hypothesis in autism Spectrum disorders. Mol Brain 11: 1. [Crossref]
2. Anwar A, Abruzzo PM, Pasha S, Rajpoot K, Bolotta A, et al. (2018) Advanced glycation endproducts, dityrosine and arginine transporter dysfunction in autism – a source of biomarkers for clinical diagnosis. Mol Autism 9:3.
3. Zaki MM, Abdel-Al H, Al-Sawi M (2017) Assessment of plasma amino acid profile in autism using cation-exchange chromatography with postcolumn derivatization by ninhydrin. Turk J Med Sci 47: 260-267. [Crossref]
4. Mavel S, Nadal-Desbarats L, Blasco H, Bonnet-Brilliout F, Barthélémy C, et al. (2013) IH-13C NMR-based urine metabolic profiling in autism spectrum disorders. Talanta 114: 95-102. [Crossref]
5. Esafoğlu E, Irene I (2018) Decreased plasma agmatine levels in autistic subjects. J Neurol Neurosurg Psychiatry 89: 735-740. [Crossref]
6. Zhao X, Chen Y, Tan X, Zhang L, Zhang H, et al. (2018) Advanced glycation end-products suppress autophagic flux in podocytes by activating mammalian target of rapamycin and inhibiting nuclear translocation of transcription factor EB. J Pathol 245: 235-248. [Crossref]
7. Varga NA, Pentelényi K, Balica P, Gézsi A, Reményi V, et al. (2018) Mitochondrial dysfunction and autism: comprehensive genetic analyses of children with autism and mtDNA deletion. Behav Brain Funct 14:4.
8. Hollis F, Kanellopoulos AK, Bagi C (2017) Mitochondrial dysfunction in Autism Spectrum Disorder: clinical features and perspectives. Curr Opin Neurobiol 45: 178-187. [Crossref]
9. Pei L, Wallace DC (2017) Mitochondrial etiology of Neurodevelopmental Disorders. Biol Psychiatry 83: 722-730. [Crossref]
10. Napoli E, Wong S, Hertz-Picciotto I, Giulivi C (2014) Deficits in bioenergetics and impaired immune response in granulocytes from children with autism. Pediatrics 133: e1405-1410. [Crossref]
11. de la Bâtie CD, Barbier V, Roda C, Brassier A, Arrous IB, et al. (2017) Autism spectrum disorders in proproteinic acidemia patients. J Inherit Metab Dis. [Crossref]
12. Frye RE, Nankova B, Bhattacharyya S, Rose S, Benucci SC, et al. (2017) Modulation of Immunological Pathways in Autistic and Neurotypical Lymphoblastoid Cell Lines by the Enteric Microbiome Metabolite Propionic Acid. Front Immunol 8:1670. [Crossref]
13. Choi J, Lee S, Won J, Jin Y, Hong Y, et al. (2018) Pathophysiological and neurobehavioral characteristics of a proprotein-activated autism-like rat model. PLoS One 13: e0192925. [Crossref]
14. Macfabe D (2013) Autism: metabolism, mitochondria, and the microbiome. Glob Adv Health Med 2: 52-66. [Crossref]
15. Morland C, Froiland AS, Petterson MN, Storm-Mathisen J, Gunderson V, et al. (2018) Propionate enters GABAergic neurons, inhibits GABA transaminase, causes GABA accumulation and lethargy in a model of proproteinic acidemia. Biochem J 475: 749-758. [Crossref]
16. Hollis F, Kanellopoulos AK, Bagi C (2017) Mitochondrial dysfunction in Autism Spectrum Disorder: clinical features and perspectives. Curr Opin Neurobiol 45: 178-187. [Crossref]
17. Patowary A, Podkrajšek KT, Lukáš MM, Bagi C (2018) Next Generation Proteomic studies identified a single nucleotide polymorphism in glyoxalase 1 as autism susceptibility factor. Am J Med Genet A 131: 11-17. [Crossref]
18. Barua M, Jenkins EC, Chen W, Kuizon S, Pullarkat RK, et al. (2011) Glyoxalase I polymorphism rs2376654 causing the Ala111Glu substitution modulates enzyme activity--implications for autism. Autism Res 4: 262-270. [Crossref]
19. Maher P (2012) Methylglyoxal, advanced glycation end products and autism: is there a connection? Med Hypotheses 78: 548-552. [Crossref]
20. Kovak J, Podkrajšek KT, Lukáš MM, Bagi C (2015) Weak association of glyoxalase 1 (GLO1) variants with autism spectrum disorder. Eur Child Adolesc Psychiatry 24: 75-82. [Crossref]
21. Rabbani N, Xue M, Thornalley PJ (2016) Methylglyoxal-induced dicarbonyl stress in aging and disease: first steps towards glyoxalase 1-based treatments. Clin Sci (Lond) 130: 1677-1696. [Crossref]
22. Allaman I, Bélanger M, Magistretti PJ (2015) Methylglyoxal, the dark side of glycolysis. Front Neurosci 9: 23. [Crossref]
23. Gabriële S, Lombardi F, Sacco R, Napoli T, Altiere L, et al. (2014) The GLO1 C332 (Ala111) allele confers autism vulnerability: family-based genetic association and functional correlates. J Psychiatri Res 59: 108-116. [Crossref]
24. Junaid MA, Kowal D, Barna M, Pullarkat PS, Sklower Brooks S, et al. (2004) Proteomic studies identified a single nucleotide polymorphism in glyoxalase 1 as autism susceptibility factor. J Med Genet A 131: 11-17. [Crossref]
25. Maher P (2012) Methylglyoxal, advanced glycation end products and autism: is there a connection? Med Hypotheses 78: 548-552. [Crossref]
26. Matsuda N, Kimura M, Quellicone BB, Kojima W, Mishima M, et al. (2017) Parkinson’s disease-related DJ-1 functions in thiol quality control against aldehyde attack in vitro. Sci Rep 7: 12816. [Crossref]
27. Ilichenko S, Ramu J, Paule MG, Hanig J (2018) Comparison of quantitative T2 and T1 relaxometry in children with autism spectrum disorder. Autism Res 11: 1. [Crossref]
28. Rose S, Bennuri SC, Wynne R (2017) Mitochondrial and redox abnormalities in autism lymphoblastoid cells: a sibling control study. FASEB J 31: 904-909. [Crossref]
29. El-Rashidy O, El-Baz F, El-Gendy Y, Khalaf R, Reda D, et al. (2017) Ketogenic diet versus gluten free casein free diet in autistic children: a case-control study. Metab Brain Dis 32: 1935-1941. [Crossref]
53. Holliday R, McFarland GA (1996) Inhibition of the growth of transformed and
61. Baraniuk JN, El-Amin S, Corey R, Rayhan R, Timbol C (2013) Carnosine treatment for
60. Szczesniak D, Budzesc S, Kopea W, Rymaszewska J (2014) Anserine and carnosine
45. Crossref
44. Crossref
43. Bertidge MJ (2018) Vitamin D deficiency: infertility and neurodevelopmental diseases
42. El-Assary A, Caneel JJ, Bjorkland G, Bhat RS, Al Dhasam AM (2018) In the search for
32. Crossref
31. Grönborg S, Holmberg E, Wibeck M, Bonnier C (2017) Advanced glycation end products and strontium ranelate promote osteogenic differentiation of vascular smooth muscle cells in vitro: Preventive role of vitamin D. Mol Cell Endocrinol 450: 94-104. [Crossref]
30. [Crossref]
29. Ding X, Stein TP, Barnes V, Rhodes N, Guo L (2012) Metabolic perturbance in autism spectrum disorders: a metabonomics study. J Proteome Res 11: 5856-5862. [Crossref]
28. Chengappa KN, Turkin SR, DeSanti S, Bowie CR, Brar JS, et al. (2012) A preliminary, randomized, double-blind, placebo-controlled trial of L-carnosine to improve cognition in schizophrenia. Randomized controlled trial of vitamin D supplementation in children with autism spectrum disorder. J Child Psychol Psychiatry 28: 74-81. [Crossref]
27. Vistoli G, Colzani M, Mazzolari A, Gilardoni E, Rivaletto C, et al. (2017) Quenching activity of carnosine derivatives towards reactive carbonyl species: Focus on a-(methylglyoxal) and ß-(malondialdehyde) dicarbonyls. Biochem Biophys Res Commun 492: 487-492. [Crossref]
26. Berridge MJ (2018) Vitamin D deficiency: infertility and neurodevelopmental diseases (attention deficit hyperactivity disorder, autism, and schizophrenia). Am J Physiol Cell Physiol 314: C135-C135E1. [Crossref]
25. Winden KD, Ebrahimi-Fakhari D, Sahin M (2018) Abnormal mTOR Activation in Autism Spectrum Disorder. J Neuroinflammation 15: 552-564. [Crossref]
24. Bopp CM, Ellingboe T, Cascarino A, Rissman EJ, King TA (2017) Proliferation of Human Gastrointestinal Carcinoma Cells by Retarding Akt/mTOR/p70S6K Signaling. J Cancer 5: 382-389. [Crossref]
23. Hipkiss AR (2018) Energy metabolism and autism: The ameliorative potential of carnosine and agmatine. Am J Physiol Cell Physiol 314: C135-C135E1. [Crossref]
22. Napoleon E, Song G, Wong S, Hagerman R (2016) Altered Bioenergetics in Primary Dermal Fibroblasts from Adult Carriers of the FMR1 Premutation Before the Onset of the Neurodegenerative Disease Fragile X-Associated Tremor/Ataxia Syndrome. Cerebellum 15: 552-564. [Crossref]
21. Zhao J, Shi L, Zhang LR (2017) Neuroprotective effect of carnosine against a-selinolenic acid-induced Parkinson’s disease. Exp Ther Med 14: 664-670. [Crossref]
20. Baek SH, Noh AR, Kim KA, Akram M, Shin YJ, et al. (2014) Modulation of mitochondrial function and autophagy mediates carnosine neuroprotection against ischemic brain damage. Stroke: 45: 2438-2443. [Crossref]
19. Oei TC, Chan KM, Sharir R (2017) Zinc L-carnosine supplementation attenuated fasting glucose, triglycerides, advanced glycation end products, and tumor necrosis factor-a levels in patients with type 2 diabetes: a double-blind placebo-controlled randomized clinical trial. Nutr Res 49: 96-106. [Crossref]
18. El-Ansary A, Cannell JJ, Bjørklund G, Bhat RS, Al Dbass AM (2018) In the search for reliable biomarkers for the early diagnosis of autism spectrum disorder: the role of vitamin D. Metab Brain Dis 33: 917-931. [Crossref]
17. Vistoli G, Colzani M, Mazzolari A, Gilardoni E, Rivaletto C, et al. (2017) Quenching activity of carnosine derivatives towards reactive carbonyl species: Focus on a-(methylglyoxal) and ß-(malondialdehyde) dicarbonyls. Biochem Biophys Res Commun 492: 487-492. [Crossref]
16. Aydin AF, Käckgörçin C, Ceban J, Dogan-Ekici I, Dogru-Abbasoglu S, (2018) Carnosine prevents testicular oxidative stress and advanced glycation end product formation in D-galactose-induced aged rats. Andrologia: 50. [Crossref]
15. Bingul, Y, Almaz, Z, Aydan AF1, Aoum J, DoiyAbru-ABBASOL Y1, S1, et al. (2017) Antiglycation and anti-oxidant efficiency of carnosine in the plasma and liver of aged rats. Geriatr Gerontol Int 17: 2610-2614. [Crossref]
14. Hoyougahani S, Kheirouri S, Faraji E, Jafarabadi MA (2018) L-Carnosine supplementation attenuated fasting glucose, triglycerides, advanced glycation end products, and tumor necrosis factor-a levels in patients with type 2 diabetes: a double-blind placebo-controlled randomized clinical trial. Nutr Res 49: 96-106. [Crossref]
13. Hipkiss AR, Preston JE, Hlimsworth DT, Wosington VC, Keown M, et al. (1998) Pluritpotent protective effects of carnosine, a naturally occurring dipeptide. Ann N Y Acad Sci 854: 37-53. [Crossref]
12. Vistoli G, Colzani M, Mazzolari A, Gilardoni E, Rivaletto C, et al. (2017) Quenching activity of carnosine derivatives towards reactive carbonyl species: Focus on a-(methylglyoxal) and ß-(malondialdehyde) dicarbonyls. Biochem Biophys Res Commun 492: 487-492. [Crossref]
11. Guo M, Zhu J, Yang T, Lai X, Lei Y, et al. (2018) Vitamin A and vitamin D deficiencies exacerbate symptoms in children with autism spectrum disorders. Nutr Neurosci 16: 1-11. [Crossref]
10. Saad K, Abdel-Rahman AA, Elserey YM, Al-Atrum AA, El-Houtey AA, et al. (2018) Randomized controlled trial of vitamin D supplementation in children with autism spectrum disorder. J Child Psychol Psychiatry 59: 20-29. [Crossref]
9. Hipkiss AR, Preston JE, Hlimsworth DT, Wosington VC, Keown M, et al. (1998) Pluritpotent protective effects of carnosine, a naturally occurring dipeptide. Ann N Y Acad Sci 854: 37-53. [Crossref]
8. Vistoli G, Colzani M, Mazzolari A, Gilardoni E, Rivaletto C, et al. (2017) Quenching activity of carnosine derivatives towards reactive carbonyl species: Focus on a-(methylglyoxal) and ß-(malondialdehyde) dicarbonyl. Biochem Biophys Res Commun 492: 487-492. [Crossref]
7. Aydin AF, Käckgörçin C, Ceban J, Dogan-Ekici I, Dogru-Abbasoglu S, (2018) Carnosine prevents testicular oxidative stress and advanced glycation end product formation in D-galactose-induced aged rats. Andrologia: 50. [Crossref]
6. Bingul, Y, Almaz, Z, Aydan AF1, Aoum J, DoiyAbru-ABBASOL Y1, S1, et al. (2017) Antiglycation and anti-oxidant efficiency of carnosine in the plasma and liver of aged rats. Geriatr Gerontol Int 17: 2610-2614. [Crossref]
5. Hoyougahani S, Kheirouri S, Faraji E, Jafarabadi MA (2018) L-Carnosine supplementation attenuated fasting glucose, triglycerides, advanced glycation end products, and tumor necrosis factor-a levels in patients with type 2 diabetes: a double-blind placebo-controlled randomized clinical trial. Nutr Res 49: 96-106. [Crossref]
4. Zhao J, Shi L, Zhang LR (2017) Neuroprotective effect of carnosine against a-selinolenic acid-induced Parkinson’s disease. Exp Ther Med 14: 664-670. [Crossref]
3. Baek SH, Noh AR, Kim KA, Akram M, Shin YJ, et al. (2014) Modulation of mitochondrial function and autophagy mediates carnosine neuroprotection against ischemic brain damage. Stroke: 45: 2438-2443. [Crossref]
2. Oei TC, Chan KM, Sharir R (2017) Zinc L-carnosine supplementation attenuated fasting glucose, triglycerides, advanced glycation end products, and tumor necrosis factor-a levels in patients with type 2 diabetes: a double-blind placebo-controlled randomized clinical trial. Nutr Res 49: 96-106. [Crossref]
1. Hipkiss AR, Preston JE, Hlimsworth DT, Wosington VC, Keown M, et al. (1998) Pluritpotent protective effects of carnosine, a naturally occurring dipeptide. Ann N Y Acad Sci 854: 37-53. [Crossref]
86. Turan I, Ozacmak HS, Ozacmak VH, Barut F, ArasÄ M (2017) Agmatine attenuates intestinal ischemia and reperfusion injury by reducing oxidative stress and inflammatory reaction in rats. Life Sci 189: 23-28. [Crossref]

87. Kim JM, Lee JE, Cheon SY, Lee JL, Kim SY, et al. (2016) The anti-inflammatory Effects of Agmatine on Transient Focal Cerebral Ischemia in Diabetic Rats. J Neurosurg Anesthesiol 28: 203-213. [Crossref]

88. Laing S, Unger M, Koch-Nolte F, Haag F (2011) ADP-ribosylation of arginine. Amino Acids 41: 257-269. [Crossref]

89. Neis VB, Moretti M, Bettio LE, Ribeiro CM, Rosa PB, et al. (2016) Agmatine produces antidepressant-like effects by activating AMPA receptors and mTOR signaling. Eur Neuropsychopharmacol 26: 959-971. [Crossref]

90. Nismi I, Horyn O, Duihink Y, Chen F, Li C, et al. (2014) The molecular and metabolic influence of long term agmatine consumption. J Biol Chem 289: 9710-9728. [Crossref]

91. Gilad GM, Gilad VH (2013) Evidence for oral agmatine sulfate safety—a 95-day high dosage pilot study with rats. Food Chem Toxicol 62: 758-762. [Crossref]

92. Schulz M, Hamprecht B, Kleinkauf H, Bauer K (1989) Regulation by dibutyryl cyclic AMP of carnosine synthesis in astroglia-rich primary cultures kept in serum-free medium. J Neurochem 52: 229-234. [Crossref]

93. Gugliucci A, Menini T (2003) The polyamines spermine and spermidine protect proteins from structural and functional damage by AGE precursors: a new role for old molecules? Life Sci 72: 2603-2616. [Crossref]

94. Ji X, Kember RL, Brown CD, BuÄan M, et al. (2016) Increased burden of deleterious variants in essential genes in autism spectrum disorder. Proc Natl Acad Sci U S A 113: 15054-15059. [Crossref]

95. Newell C, Bomhof MR, Reimer RA, Hittel DS, Rho JM, et al. (2016) Ketogenic diet modifies the gut microbiota in a murine model of autism spectrum disorder. Mol Autism 7: 37. [Crossref]

96. Alarcón-Herrera N, Flores-May S, Bellido B, García-Bores AM, Mendoza E, et al. (2017) Protective effects of chlorogenic acid in 3-nitropropionic acid induced toxicity and genotoxicity. Food Chem Toxicol 109: 1018-1025. [Crossref]

97. Kalkbrenner AE, Windham GC, Zheng C, McConnell R, Lee NL, et al. (2018) Air Toxics in Relation to Autism Diagnosis, Phenotype, and Severity in a U.S. Family-Based Study. Environ Health Perspect 126: 037004. [Crossref]

98. Fadda LM, Attia HA, Al-Rasheed NM, Ali HM, et al. (2017) Attenuation of DNA damage and mRNA gene expression in hypoxic rats using natural antioxidants. J Biochem Mol Toxicol 31. [Crossref]

99. Laube G, Bernstein HG (2017) Agmatine: multifunctional arginine metabolite and magic bullet in clinical neuroscience? Biochem J 474: 2619-2640. [Crossref]

100. Hipkiss AR (2018) Glycotoxins: Dietary and Metabolic Origins; Possible Amelioration of Neurotoxicity by Carnosine, with Special Reference to Parkinson’s Disease. Neurotox Res [Crossref]

101. Tsai SJ, Kuo WW, Liu WH, Yin MC (2010) Antioxidative and anti-inflammatory protection from carnosine in the striatum of MPTP-treated mice. J Agric Food Chem 58: 11510-11516. [Crossref]

102. Kawahara M, Tanaka KI, Kato-Negishi M (2018) Zinc, Carnosine, and Neurodegenerative Diseases. Nutrients 10. [Crossref]

103. Herculano B, Tamura M, Ohba A, Shimatani M, Kutsuna N, et al. (2013) ß-alanyl-L-histidine rescues cognitive deficits caused by feeding a high fat diet in a transgenic mouse model of Alzheimer’s disease. J Alzheimers Dis 33: 983-987. [Crossref]

104. Hipkiss AR (2007) Could carnosine or related structures suppress Alzheimer’s disease? J Alzheimers Dis 11: 229-240. [Crossref]