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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. Both carnosine and agmatine levels in sera of autistic individuals are reported to be lower than in control subjects. Carnosine and agmatine can influence cellular energy metabolism, in part via effects on mTOR, thereby decreasing glycolysis and enhancing mitochondrial activity and thus countering onset of Warburg-like metabolism: other mechanisms including suppressing methylglyoxal toxicity are also discussed. Dietary supplementation studies with carnosine and arginine (agmatine precursor) indicate ameliorative activity towards behaviour in ASD subjects. It is suggested that co-administration of carnosine and agmatine should be explored as a potential route for ASD amelioration.

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 PI3AktmTOR 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, propionic acid inhibits GABA breakdown causing its accumulation [15] thereby affecting brain function. Interestingly, raised levels of β-alanine have been detected in the urine of some autistic subjects [4], whilst in other autistic individuals a decrease was detected [3]. These observations, although seemingly contradictory, may reflect differences in β-alanine generation and utilisation by the micro-organisms in the gut. β-Alanine is a precursor of pantothenic acid which, in turn, is a precursor of Co-enzyme-A (CoA) (synthesized by the gut micro-organisms). The microbiome is the predominant source of pantothenic acid in the human body. One speculative suggestion is that propionic acid accumulates as a result of a failure in its carboxylation, which requires functional CoA, hence propionic acid accumulates if synthesis of Co-A is compromised. General deficiency in CoA availability would also decrease fatty acid oxidation, as found in ASD [7,10,16-18]. The resultant mitochondrial dysfunction would have two important consequences which directly impact ASD. First, the decreased supply of electrons (i.e. acetyl units attached to CoA) will provoke an increase in the generation of incompletely reduced oxygen molecules, i.e. oxygen free-radicals [19], the presence of which will provoke formation of deleterious reactive oxygen species (ROS) and reactive nitrogen species (RNS). Such a mechanism may account for the raised levels of protein oxidation and nitration recently detected in autistic patients' urine and plasma [2]. A second consequence of insufficient mitochondrial ATP synthesis may be a compensating upregulation of glycolysis in an attempt to maintain ATP levels [1]. Indeed enhanced glycolysis accompanied by mitochondrial abnormalities have been detected in ASD subjects (compared to siblings and controls) [20]. Importantly, upregulated glycolysis would enhance generation of the highly toxic bicarbonyl

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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 glycating 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 oxidized, nitrated and glycated proteins.

There is additional evidence that ASD may be associated directly with changes in energy metabolism. A number of studies showing that the anti-aging agent rapamycin, 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 Nfr2 expression and/or function [75,76]. Furthermore, it should be noted that carnosine may mimic rapamycin to some degree in its ability to inhibit mTOR activity [77]; as noted above, rapamycin 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 glycated 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 glycolysis, 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.

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