Milk metabolites and neurodegeneration: Is there crosstalk?

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ABSTRACT

Milk has been considered as a natural source of nutrition for decades. Milk is known to be nutrient-rich which aids the growth and development of the human body. Milk contains both macro- and micronutrients. Breast milk is widely regarded as the optimal source of neonatal nutrition due to its composition of carbohydrates, proteins, minerals and antibodies. However, despite the wide use of milk products, investigations into the role of milk in degenerative diseases have been limited. This review will examine the relationship between the β-casein gene found in bovine milk and disease states by using age-related macular degeneration as an example.

KEYWORDS: Milk metabolism, A1/A2 alleles, β-casein, Opioid receptors, BCM-7

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Introduction

Types of milk

Milk has been an important source of nutrition for several decades. Humans have been rearing animals for milk since the beginning of time/ beginning of history. Recently, interesting results from milk protein efficacy studies has reignited the need to examine the biological effects of proteins obtained from milk. RB Elliot and his group described that bovine milk may contribute to the risk of type 2 diabetes mellitus as well as heart disease. They conducted a study in Polynesian children with diabetes and found increased antibody levels against cow milk.[1] The suspected antigen was β-casein, a protein which is common constituent of milk from all species. A genetic study by same group showed the impact of different variants of β-casein gene.[2]

Immunoreactivity of milk metabolites

A review of the relevant literature indicates that the β-casein gene has 12 genetic variants, out of which the A1 and A2 genetic variants are most studied with respect to different diseases in human population. Although A1 and A2 differ from each other only by difference of one amino acid, their health outcomes are different.[3] In 2003, it became known to the public for first time that there are three types of cow'smilk, namely type A1, A2 and A1/A2 mixed. In 1995 theNew Zealand investigators of A2 Corporation Limited filed a patent (ID No: EP19950937232). This patentpostulated a mechanism to distinguish between the A1 and A2 milk types, which became known later as the diabetogenic and non-diabetogenic milk types. The patent applicationstarted a series of studies in milk research through the following claims.. The patent claimed that the A2, A3, D and E β-caseinvariants are non-diabetogenic variant of milk, with A2 being the preferred variant. The A1, B, C and F variants are diabetic, with the A1 variant being the most diabetogenic. A1 milk could be identified with chromatography screening for the presence of the hexapeptide Pro-Gly-Pro-Ile-His-Asn.. The nature of milk in a specific breed of cattle may be heritable. This patent lead to the practice of selling selected milk.[4] Later in 1998, another patent filed by New Zealand dairy board and New Zealand child health research foundation stated A1 milk triggers a beneficial immunogenic response.[5] These patents were the basis of separate marketing and selling ofA1 and A2 milk variants. Digestion of our food starts from our mouth. However, casein is not digested in mouth, but it immediately dissolves in gut enzymes. The peptides forming up after the breakdown of casein are shown to have positive immunoreactivity towards immunoglobulin (Ig) E,G,G4 or A. The levels of immunoreactivity after casein digestion may vary from variant to variant. As in case of Beta casein the reactivity levels are minimised towards the end of digestion, whereas it may be different story in case of alpha casein. As the immune reactivity depends on the epitopes, the changes in genetic variants of peptides arising out of casein digestions may modify the whole immunoreactions in body.[6,7] Recently as tudy in 2014 conducted a test to identify the role of IgA and TGF beta specific to casein in Food protein-induced enterocolitis syndrome (FPIES) to milk a gastro intestinal hypersentivity disorder in children. The study showed the minimal titer levels for IgG and IgA and absence of TGF beta levels stating tGF beta as a possible biomarker whose lowering levels may indicate the person being affect by (FPIES).[8]

Factors responsible for the A1 or A2 variant of milk

Genetic Variations

Over the last decade, various studies have documented the two types of milk. In 2003, Tailforde*t al.* reported that the presence of A1 and A2 variants is largely affected by thecattlebreed.[9] However, the role of epidemiological and etiological factors in milk type requires further investigation. In 2009, a group of researchers led by Olenski stated breeding as a reason for variation in β-casein milk protein. A regression model was used to study the association between the breeding values and milk variant. Genotyping of breeding bulls for A1 and A2 allele was suggested as an important precaution for lowering the risk of A1 allele in human health.[11] Below is the table consisting of studies carried out in different breeds animals.

Table 1. Table of studies involving different genes.

Is β-casein conserved in mammals?

Does β-casein gene impact all animalspecies ? In 1990 a Danish group published a report about the genetic polymorphisms for different proteins found in milk in 4 different breeds namely Danish Jersey,

Table 1: Studies depicting the analysis of polymorphisms in different genes for their polymorphisms

S. No.	Study	Animal Breed	Factor	Genes Scanned	Reference
1.	Polymorphism of the beta-casein gene and its association with breeding value for production traits of Holstein–Friesian bulls	Holstein–Friesian bulls	Breeding	None	[11]
2.	Milk protein polymorphism in Danish dairy cattle and the influence of genetic variants on milk yield	Danish Jersey, Red Danish Dairy Cattle (RDM), and Black and White Danish Dairy Cattle (SDM)	Genetic Polymorphism	αs1, β and K-cascin and β-lactoglobulin (β-Lg)	[12]
3.	Effects of genetic variants in milk protein on yield and composition of milk from Holstein-Friesian and Simmentaler cows	Holstein-Friesian (HF) and Simmentaler cows	Genetic polymorphism	αS1-, β- and κ-caseins (Cn) and β-lactoglobulin (-Lg)	[13]
4.	Milk protein genes CSN1S1, CSN2, CSN3, LGB and their relation to genetic values of milk production parameters in Czech Fleckvieh	Czech Fleckvieh	Genetic polymorphisms	alphaS1-casein (CSN1S1), beta-casein (CSN2), kappa-casein (CSN3) and beta-lactoglobulin (LGB)	[14]
5.	Detection of milk protein genetic polymorphisms in order to improve dairy traits in sheep and goats: a review	Sheep, Goat	Genetic polymorphisms	α-s1 and α-s2 casein, β-casein, κ-casein, β-lactoglobulin and α-lactalbumin	[17]
6.	Milk protein polymorphisms in Holstein cattle	Holstein Cattle	Genetic Polymorphisms	α_{s1}-casein, β-casein, κ-casein and β-lactoglobulin	[18]

Red Danish Dairy Cattle (RDM), and Black and White Danish Dairy Cattle (SDM). The authors argued in the paper that the levels of 4 proteins i.e αs1, β and K-caesin and β-lactoglobulin (β-Lg) were variable in all the four breeds they studied.[11] However, from earlier studies it is also evident that the effects of β-casein also varies from animal to animal. In 1999, a study by the Elliot group showed the relationship between A1 β-casein form and incidence of diabetes. The group compared the data for diabetic patients, ranging from 0–14 years of age, from 10 different countries with a high cattle milk consumption. The group reported that the A1 variant formed Beta Casomorphin-7, which largely affected the opioid activity of different endogenous bio-chemicals. The A1 variant is absent in human and goat's milk – which are both rich in the A2 casein variant.[2] Some researchers have compared the effect of ' A1 and A2 milk metabolites on atherosclerosis in a rabbit model.[9] In 1986, a report by Obaid Ullah Beg confirmed the presence of β-casein protein in camel milk. β-casein Later,[10] Salami *et al.* reported camel milk β-casein as a good source of safe antioxidants which is easy to digestThe authors also postulated that camel milkinhibits the Angiotensin Converting Enzyme (ACE).[19] which regulates blood pressure.[20] Similarly in 2014 another group reported the increase ACE inhibitory activity of betacasein in bovine milk. The digestion of casein from bovine milk lead to increased levels of antioxidants as well as significant decrease in ACE expression thus pointing to conservatory phenomenon with respect to casein in mammals through evolution.[15] A comparison of the the α-s1, α-s2, β, and κ-casein, β-lactoglobulin and α-lactalbumin polymorphisms in sheep and goats show that. how the change in gene structure may impair the quality of cheese and milk product in both the animals. Polymorphisms are the quality determining factor of milk produced and they can impact the choice of breeding in mammals at invitro levels thus signifying the importance of common genetic pattern of casein gene in both mammals.[11] The phenomenon of casein common activity can be owed to the conservation of gene sequence in mammals. As reported by Kaimala in 2015 the author has identified the gene present in locus of casein. The authors reported the presence of Evolutionary conserved sequence in vicinity of ODAM gene in almost all the mammals.[16]

Milk metabolism and Opioid receptors

Human milk consists of approximately 20–40% casein protein.[3] Human milk is known to contain β-casein. β-casein has 13 allelic forms, out of which A1/A2 is most studied.[3] Polymorphisms in A1 β-casein are associated with risk factors of several syndromes and neurological disorders. Metabolism of A1 form of β-casein leads to formation of β-Casomorphin, also popularly called as BCM7.[21] BCM7 and lactoferrins are known to have opioid activity.[22,23] Lactoferrins are derived from whey proteins, another constituent of milk. The opioids are a class of psychoactive drugs which include morphine. Opioids are derived exogenously through food intake. Stimulation of the opioid receptors is responsible for its activity. These receptors are mostly found in both in central nervous system (CNS) and Peripheral Nervous

Systems (PNS) as well as the duct area regulated by mu opioid receptor.[23,24] Disruption of opioid activity may alter the the oxidation state of a cell. In 2006, Li *et al.* showed that endogenous opioids play a protective role in reducing the Low Density Lipoprotein (LDL)- associated oxidative stress levels in the human brain.[25–27] However, contrary to this, certain other studies show that opioid involvement hampers the oxidation balance and may lead to generation of oxidative stress.[28,29]

Cholesterol is one of the major risk factors of heart disease. Cholesterol is one of the main metabolites of milk protein. It takes on the form of either beneficial High Density Lipoprotein or damaging LDL. In 2003, Laugeseninvestigated the correlation between the milk metabolite A1, Ischemic heart disease and Type 1 diabetes. The study showed a strong correlation between A1 bovine milk and ischemic heart disease (IHD). The data from 20 different countrieswas comparable. However, a serum cholesterol analysis did not findasignificant relationshipbetween cholesterol and A1-rich bovine milk. The group showed that A1 bovinemilk had significant a correlation with IHD-related mortality, which was ascribed to genetic variability in the cow population.[26] Previously, in 1998, Estévez-Gonzálezanalyzed the LDL and serum cholesterol levels in population of with an age group of 3-9 years. The investigators showed that serum cholesterol levels and LDL levels, arehigher in the group which consumed whole milk. When the whole milk was replaced with fat free milk with oleic acid supplementation, serum cholesterol and LDL levels decreased. The caloric content of fat free milk and whole milk was comparable.

A1/A2 role in Age Related Macular Degeneration (AMD) pathogenesis

The A1 and A2 milk metabolites are associated with diabetes and age related disorders, such as.....reference. One such a disorder is age-related macular degeneration (AMD). AMD is the leading cause of blindness in the elderly. This disease is characterised by loss of vision in central field i.e. macula. This loss occure due to damage of retina. Retina is a structure in an eye which is composed of nerves and is responsible for sending light signals to brain. It is also called as part of CNS, thus bringing the AMD under the catogery of neurodegenerative disease.[30] Numerous studies have shown that inflammation plays a large role in the pathogenesis of AMD (Telander*et al.*, 2011). Although the relationship between the A1 andA2 alleles and AMD has not been established, studies have shown that A1/A2 to regulates the expression of AMD inflammatory markers. AMD is worsened by vascularization and this causes irreversible vision loss. Certain metabolites, such as (insert metabolite here) affects AMD progressionthrough altering the expression of Vascular Endothelial Growth Factor VEGF. Milk metabolites may have therapeutic benefits for retinal degeneration. Studying these effects with models of retinal degeneration will open a therapeutic window for the use of nutritional supplements in degenerative diseases.

AMD is a complex aging-related disorder, with a multifactorial progression profile. Investigating the role of environmental factors could shed light on this subjectA possible environmental cause are dietary lipids. Lipids are an important constituent of milk. Studies suggest that high lipid intake may increase the risk of developing AMD.[31–33] Mutations in the Lipase, Hepatic (*LIPC)* gene, which encodes triglyceride lipase, is a known risk factor for AMD.[34] Similarly, other genes like Apolipoprotien E *APOE*,[35] Cholesteryl ester transfer protein *CETP*[36] are also known to be involved in lipid metabolismand the pathogenesis of other age-related disorders such as Alzheimer's disease. APOE protien is derived in liver and is responsible for transport of cholesterol to neurons to provide the myelin covering sheath and protect them from degeneration. APOE has 4 main variants out of which variant 4 is found to be highly associated with patients of Alzheimer's disease. This may be due to APOE high binding affinity to Beta Amyloid plaques thus leading to memory loss. However in relation to AD amyloid beta plaques find a common role in both AD and AMD due to its presence in both brain as well as drusen an extracellular deposit between retinal pigment epithelium and Bruch's membrane.[37–39] For the last two decades the link between AMD and APOE has been a subject ofcontroversy. l. In 1998, a study linked theAPOE epsilon 2 variant with AMD at genetic level.[40] In 1998, Zarbin stated that APOE was involved in pathogenesis of AM D.[41] In 2011, Gareth *et al.* performed a pooled analysis to estimatethe risk conferredby APOE variants in pathogenesis of AMD. The study reported that the APOE 4 variant protects against AMD and APOE2 is a risk factor for late-onset AMD.[42] Other studies found similar results.[40,42–44] Mutations in these genes increases the levels of lipoproteins metabolized from lipids which increases cellular oxidative stress. These lipoproteins are further oxidisedby BCM7, thus increasing oxidative stress.[45] Reactive Oxygen Species (ROS) activate Hypoxia inducible factor 1α (HIF-1 alpha). HIF-1 alpha activates VEGF to initiate vascularisation which contributes to the pathology of AMD. Lactoferrin, another compound, from whey protein gives rise to Lactoferricin B LfcinB. LfcinBbinds to the heparin binding site of endothelial cells, through competitive inhibition of VEGF. This prevents angiogenesis,[46] which is beneficial for AMD. The matrix metalloproteinases (MMPs) are a group of compounds involved in the degeneration of the extra cellular matrix. These compounds are regulated by TIMP metallopeptidase inhibitor 3 TIMP3. TIMP3 is localized in humanretinal pigment epithelium (hRPE) AMD.[47] Dipeptidyl peptidase-4 (DPP4), is an enzyme involved in metabolism of β-casein. Inhibition of DPP4 has been shown to reduce the expression of MMP2 and thus DPP4 inhibition may have a protective role in AMD.[48] A reduction of DPP4 is also associated with improved cardiovascular health. Recently on 2014 an animal study in wistar rats reported the association of beta casein variant A1 with DPP4 activation and high inflammation, thus indicating that higher levels of DPP4 in association with Beta Casein A1 variant may lead to increased inflamtory response in body.[49] Several *invitro* studies have shown that DPP4 increases vascularisation through Neuropeptide Y (NPY) signalling. DPP4 converts NPY to a shorter form, NPY3-36, which is responsible for angiogenesis. This review of the literature indicates that the correlation between milk metabolism and age related disorders needs to be more thoroughly investigated. This review has focussed on vascularisation events which are important role in the pathogenesis of AMD. AMD is hypothesised to be regulated by metabolites of milk proteins. The casein and whey protein milk metabolites share acommon pathway in the molecular pathogenesis of AMD (Figure 1)

Conclusion

Vascularisation is an important event in AMD.[50–52] The review explores how the milk metabolites could influence vascularisation and cause AMD to improve the understanding of. role of nutrition in AMD. Vascularisation is involved in the pathogenesis of numerous degenerative

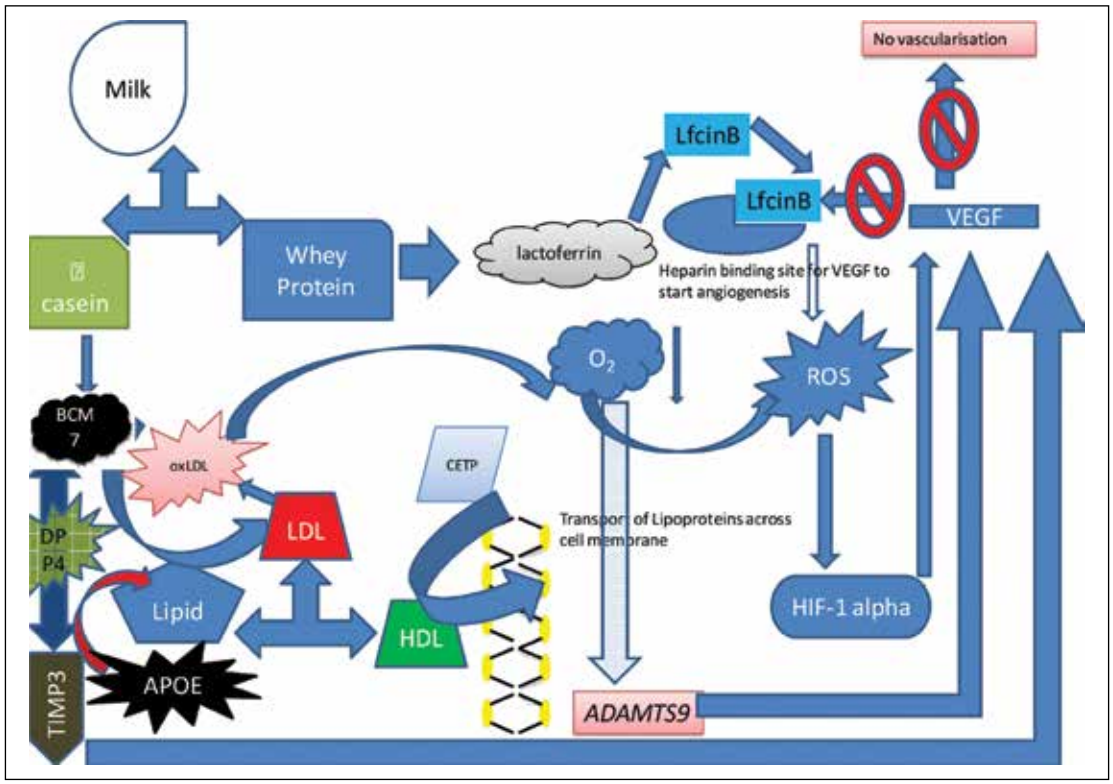

Fig. 1: Central role of vascularisation in crosstalk between different disease markers of AMD with milk protein.

disorders. One of these disorders, is amytrophic lateral sclerosis (ALS), a rapidly fatal neurodegenerative disease.[53–55] Vascularization may improve the survival of of dying neurons. The HIF-1 alpha pathway increases vascularization during times of oxidative stress y.[56] This review hypothesises the role of milk metabolites in hindering the expression of vascularisation. The milk metabolites may have different roles in the pathogenesis of different diseases and thus be beneficial in certain diseases and detrimental in others. There is an imperative need to study role of nutrition in different diseasesto understand the mechanisms by which nutrition alters the outcomes of aging.

Nutrition is a key constituent of our environment. Understanding of the role of nutrition is critical to improve understanding of degenerative diseases like AMD. Milk, which is widely regarded as an important constituent in early life, has been shown to deliberately affect our health. In order to ascertain the role of milk consumption in progression of this degenerative disease, it is imperative that the two alleles (A1 and A2) and their metabolic products be examined in relation with pathophysiology of the AMD.

Authors Contribution

Akshay Anand: Made substantial contributions to conception and design of manuscript, and gave final approval for publication of manuscript, **Keshav Thakur:** Has been involved in drafting the manuscript

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