# Milk Proteins and Human Health: A1 versus A2 Beta-casein

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***An Address to the General Practitioners Conference, Sydney, 22 May 2011***

## Background Science

1. The issues relate to a peptide called beta-casomorphin-7 (BCM7). This peptide is released on digestion from A1 beta-casein. BCM7 is not released on digestion from A2 beta-casein (1).

2. Beta-casomorphin-7 (BCM7) is a hepta-peptide with opioid characteristics and a strong affinity for mu-opioid receptors. Its derivative BCM5 has even stronger opioid activity (2).

3. Most milk in Australian supermarkets contains a mix of A1 and A2 beta-casein and is commonly referred to as 'A1 milk'. Milk in which more than 99% of the beta-casein is the A2 variant is known as 'A2 milk'.

4. The original beta-casein protein in bovine milk was A2. A1 beta-casein is a consequence of a mutation, probably occurring some thousands of years ago, which is carried by a proportion of cows of European breeds (3).

5. The difference in A1 and A2 beta-casein is the amino acid histidine rather than proline at position 67 (4).

6. Human milk, goat milk, sheep milk and other species are 'A2- like' with proline at the equivalent position (5-7).

7. Susceptibility to BCM7 related health conditions is linked to the peptide being able to pass from the digestive system to the circulatory system.

8. All babies have permeable digestive systems and are therefore particularly susceptible to BCM7 passing through to the circulatory system. 'Tight junctions' that reduce passage of BCM7 form progressively during and subsequent to the first 12 months of age.

9. At-risk children and adults are those who, for any of a range of reasons, have a 'leaky gut'. This may be associated with conditions such as stomach ulcers, ulcerative colitis, Crohn's disease and Coeliac disease. Antibiotic treatment and viruses may also affect this permeability.

10. The only known enzyme that can break down BCM7 is dipeptidyl peptidase 4 (DPP4). This enzyme is found on mesenteric cells lining the digestive system. DPP4 is also found in the blood and other tissues (8, 9).

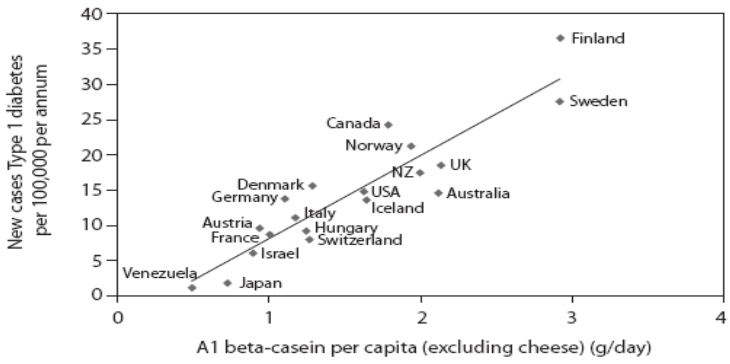
11. Low levels of DPP4 are likely to be an additional risk factor for BCM7-related conditions. These low levels may be due to genetic factors; alternatively they may be caused by artificial reduction through DPP4 inhibiting drugs (such as those used in the treatment of Type 2 diabetes).

12. There are more than 250 medical and scientific papers relating to casomorphins and their effects on the PUBMED database (search on 'casomorphin' at http://www.ncbi.nlm.nih.gov/pmc/ ).

## Health Conditions

1. Type 1 diabetes

   Evidence linking A1 beta casein to Type 1 (insulin-dependent) diabetes includes major differences in incidence between individual countries within the developed world (i.e. countries with similar lifestyles). These differences correlate remarkably with A1 beta-casein intake of these populations (10). Alternative hypotheses are unable to explain this. Supportive evidence comes from animal trials, evidence linking IDDM to milk exposure in general (11-13) and A1 beta-casein in particular (14, 15). The increasing incidence of Type 1 diabetes over time is likely to be a function of issues affecting gut permeability or antigenic susceptibility (viruses, antibiotics, hygiene factor, Vitamin D etc) rather than the quantity of A1 beta-casein *per se*.

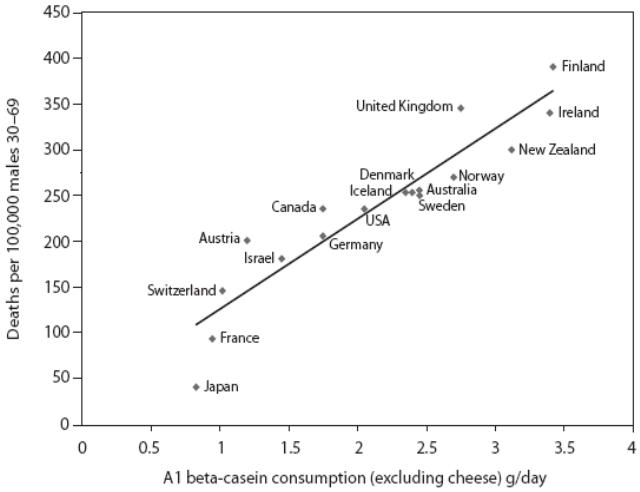



(Data from Laugesen and Elliott (10)

2. Heart disease.

   As with Type 1 diabetes, major differences in incidence between countries within the developed world correlate remarkably with A1 beta-casein intake (10, 16). In babies, formula-fed babies have been shown to have high antibodies to oxidised LDL (17). In piglets, a direct trial comparison has shown a statistically significant 'cause and effect' relationship between A1 beta-casein intake and oxidised LDL antibodies (18). In rabbits, a 'cause and effect' relationship has been shown with A1 beta-casein leading to a statistically significant build-up of arterial plaque (19). In humans, it has long been recognised that high milk diets

for stomach ulcer sufferers (a potential cause of stomach permeability) lead to high death rates from heart disease (20).




Ischaemic Heart Disease Death Rates

(Source: MacLachlan CN (16))

3. Child development

   Russian scientists have shown that BCM7 enters the blood of babies fed milk formula diets (21). Whereas some babies can quickly metabolise the BCM7, others are slow metabolisers. In babies whose BCM7 levels in the blood stay high between feeds, there is a high risk of delayed psychomotor development (21).

4. Sudden Infant Death Syndrome (SIDS)

   BCM7 has been suspected as a risk factor for SIDS for more than 20 years (22). Casomorphins have been found in the brainstems of children who have died from SIDS (23) but comparisons with normal children are obviously not possible. Until recently, direct evidence of apnoea-inducing effects was only available from animals (24). However, specific evidence of BCM7 causing respiratory depression in humans has now come from Polish scientists who have shown that babies who suffer acute life threatening events (ALTE) through apnoea are characterised by circulating levels of BCM7 that are three times higher than in normal children (8). These same children have DPP4 levels (the enzyme that degrades BCM7) that are only 58±3% of those in normal children. The evidence is that even if the babies are breast-fed, bovine BCM7 is still found in the blood of the infants. This suggests bovine BCM7 is transferring from the mother's stomach to her infant via human milk. Other work by this group has found bovine BCM5 (a stronger opioid which is derived from BCM7) in the blood of breast-fed children (25).

5. Autism

   Autism is best viewed as a spectrum of conditions. BCM7 has long been considered a risk factor for autism but the hypothesis remains controversial. Trials with animals show that BCM7 crosses the blood-brain barrier and leads to autistic type behaviour (26). Milk elimination trials in humans have produced positive results (27, 28) but are often criticised for lack of double blind protocols. Many autistic children suffer from digestive complaints

which may make them susceptible to BCM7 absorption (29). There are theoretical grounds to suspect that BCM7 reaching the brain will affect the seratoninergic system with implications for neurological development (21).

6. Intolerances
   Many people who drink A2 milk do so because they find it is easier to digest. However, A2 milk does contain lactose, which is often stated as the most important milk intolerance issue. The likely explanation for this apparent contradiction is twofold. First, the BCM7 that is released from A1 beta-casein slows down the passage of food through the digestive system (as do other opioids) providing longer time for lactose fermentation (Given that fermentation is an exponential process, a modest slowing down can lead to major production of gas and other fermentation products.) Second, many people are intolerant specifically to the BCM7. A simple test to investigate whether someone who is intolerant to 'ordinary' cows' milk will be able to drink 'A2 milk', is to ask them whether they can tolerate goats' milk. If the answer is 'yes', then my experience is that they can also tolerate A2 milk.

7. Mild allergies
   In theory, an allergy is quite distinct from an intolerance. An allergy is an immune-based condition defined by The National Institute for Allergy and Infectious Diseases (NIAID) as "*an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food*" (30). In contrast, an intolerance does not involve an immune response. In practice, they often run together, with the intolerance apparently being a consequential response. Mild allergies associated with BCM7 can include eczema and asthma, with much of the evidence being case-related. BCM7 is also known to induce production mucins (the sticky proteins in mucus) (30-33) and this provides a logical explanation for why many people associate milk with mucus production. Of course both A1 and A2 milk contain a range of proteins unrelated to BCM7 which can cause severe reactions including anaphylactic shock in susceptible people.

**Industry Options**

If the dairy industry so wished, it could breed out A1 beta-casein from the national herd over a period of 10 years, and do so at minimal cost (34). In the meantime, milk free of A1 beta-casein (i.e. 'a2 Milk™' and goat milk) is widely available. Some infant formulas that are free of all casein are available as specialist products, but an A2 infant formula is not yet available. Neither is it currently possible to purchase either ice cream or cheese made from A2 milk.

**For further information on all of the above issues refer to:**
**Woodford, Keith 2010. 'Devil in the Milk. Illnesss, health and politics'. Updated Edition. Craig Potton Publishing, Nelson**.

**For ongoing updates, refer to http://keithwoodford.wordpress.com**

## References


1. De Noni I. Release of b-casomorphins 5 and 7 during simulated gastro-intestinal digestion of bovine b-casein variants and milk-based infant formulas. Food Chemistry 2008 110(4):897-903.
2. Meisel H, FitzGerald RJ. Opioid peptides encrypted in intact milk protein sequences. Br J Nutr. 2000 Nov;84 Suppl 1:S27-31.
3. Ng-Kwai-Hang KF, Grosclaude F. Genetic polymorphism of milk proteins. In: Fox PFaM, P.L.H editor. Advanced Dairy Chemistry: Volume 1: Proteins, Parts A&B. New York: Kluwer Academic/Plenum Publishers; 2002. p. 739-816.
4. Brantl V, Teschemacher H, editors. Beta-Casomorphins and Related Peptides: Recent Developments 1994.
5. accession embl. Goat beta-casein [cited 2011 27 Apr]; Available from: http://www.ncbi.nlm.nih.gov/nuccore/AJ011019.3?
6. Lonnerdal B, Bergstrom S, Andersson Y, Hjalmarsson K, Sundqvist AK, Hernell O. Cloning and sequencing of a cDNA encoding human milk beta-casein. FEBS Lett. 1990 Aug 20;269(1):153-6.
7. Provot C, Persuy MA, Mercier JC. Complete nucleotide sequence of ovine beta-casein cDNA: inter-species comparison. Biochimie. 1989 Jul;71(7):827-32.
8. Wasilewska J, Sienkiewicz-Szlapka E, Kuzbida E, Jarmolowska B, Kaczmarski M, Kostyra E. The exogenous opioid peptides and DPPIV serum activity in infants with apnoea expressed as apparent life threatening events (ALTE). Neuropeptides. 2011 Feb 18.
9. Mentlein R. Dipeptidyl-peptidase IV (CD26)--role in the inactivation of regulatory peptides. Regul Pept. 1999 Nov 30;85(1):9-24.
10. Laugesen M, Elliott R. Ischaemic heart disease, Type 1 diabetes, and cow milk A1 beta-casein. N Z Med J. 2003 Jan 24;116(1168):U295.
11. Beales PE, Elliott RB, Flohe S, Hill JP, Kolb H, Pozzilli P, et al. A multi-centre, blinded international trial of the effect of A(1) and A(2) beta-casein variants on diabetes incidence in two rodent models of spontaneous Type I diabetes. Diabetologia. 2002 Sep;45(9):1240-6.
12. Elliott RB, Martin JM. Dietary protein: a trigger of insulin-dependent diabetes in the BB rat? Diabetologia. 1984 Apr;26(4):297-9.
13. Elliott RB, Reddy SN, Bibby NJ, Kida K. Dietary prevention of diabetes in the non-obese diabetic mouse. Diabetologia. 1988 Jan;31(1):62-4.
14. Monetini L, Cavallo MG, Manfrini S, Stefanini L, Picarelli A, Di Tola M, et al. Antibodies to bovine beta-casein in diabetes and other autoimmune diseases. Horm Metab Res. 2002 Aug;34(8):455-9.
15. Padberg S, Schumm-Draeger PM, Petzoldt R, Becker F, Federlin K. The significance of A1 and A2 antibodies against beta-casein in type-1 diabetes mellitus. Dtsch Med Wochenschr. 1999 Dec 17;124(50):1518-21.
16. McLachlan CN. beta-casein A1, ischaemic heart disease mortality, and other illnesses. Med Hypotheses. 2001 Feb;56(2):262-72.
17. Steinerova A, Korotvicka M, Racek J, Rajdl D, Trefil L, Stozicky F, et al. Significant increase in antibodies against oxidized LDL particles (IgoxLDL) in three-month old infants who received milk formula. Atherosclerosis. 2004 Mar;173(1):147-8.
18. Steinerova A, Stozicky F, Korotvicka M, Racek J,Tatzber, F. Does artificial suckling nutrition pose a risk of atherosclerosis at old age. Cesko Slovenska Pediatria 2006; 61(9):519-23.
19. Tailford KA, Berry CL, Thomas AC, Campbell JH. A casein variant in cow's milk is atherogenic. Atherosclerosis. 2003 Sep;170(1):13-9.
20. Briggs RD, Rubenberg ML, O'Neal RM, Thomas WA, Hartroft WS. Myocardial infarction in patients treated with Sippy and other high-milk diets: an autopsy study of fifteen hospitals in the U.S.A. and Great Britain. Circulation. 1960 Apr;21(4):538-42.
21. Kost NV, Sokolov OY, Kurasova OB, Dmitriev AD, Tarakanova JN, Gabaeva MV, et al. Beta-casomorphins-7 in infants on different type of feeding and different levels of psychomotor development. Peptides. 2009 Oct;30(10):1854-60.
22. Hedner J, Hedner T. beta-Casomorphins induce apnea and irregular breathing in adult rats and newborn rabbits. Life Sci. 1987 Nov 16;41(20):2303-12.
23. Pasi A, Mahler H, Lansel N, Bernasconi C, Messiha FS. beta-Casomorphin-immunoreactivity in the brain stem of the human infant. Res Commun Chem Pathol Pharmacol. 1993 Jun;80(3):305-22.
24. Sun Z, Zhang Z, Wang X, Cade R, Elmir Z, Fregly M. Relation of beta-casomorphin to apnea in sudden infant death syndrome. Peptides. 2003 Jun;24(6):937-43.
25. Wasilewska J, Kaczmarski M, Kostyra E, Iwan M. Cow's-milk-induced Infant Apnoea With Increased Serum Content of Bovine beta-Casomorphin-5. J Pediatr Gastroenterol Nutr. 2011 Apr 7.

26. Sun Z, Cade JR. A Peptide Found in Schizophrenia and Autism Causes Behavioral Changes in Rats. Autism. 1999;3(1 ):85-95
27. Knivsberg AM, Reichelt KL, Hoien T, Nodland M. A randomised, controlled study of dietary intervention in autistic syndromes. Nutr Neurosci. 2002 Sep;5(4):251-61.
28. Whiteley P, Haracopos D, Knivsberg AM, Reichelt KL, Parlar S, Jacobsen J, et al. The ScanBrit randomised, controlled, single-blind study of a gluten- and casein-free dietary intervention for children with autism spectrum disorders. Nutr Neurosci. 2010 Apr;13(2):87-100.
29. Cade JR, Privette MR, Fregly M, Rowland N, Sun Z, Zele V, et al. Autism and Schizophrenia: Intestinal Disorders. Nutr Neurosci. 2000;3:57-72.
30. Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. J Allergy Clin Immunol. 2010 Dec;126(6 Suppl):S1-58.
31. Claustre J, Toumi F, Trompette A, Jourdan G, Guignard H, Chayvialle JA, et al. Effects of peptides derived from dietary proteins on mucus secretion in rat jejunum. Am J Physiol Gastrointest Liver Physiol. 2002 Sep;283(3):G521-8.
32. Trompette A, Claustre J, Caillon F, Jourdan G, Chayvialle JA, Plaisancie P. Milk bioactive peptides and beta-casomorphins induce mucus release in rat jejunum. J Nutr. 2003 Nov;133(11):3499-503.
33. Zoghbi S, Trompette A, Claustre J, El Homsi M, Garzon J, Jourdan G, et al. beta-Casomorphin-7 regulates the secretion and expression of gastrointestinal mucins through a mu-opioid pathway. Am J Physiol Gastrointest Liver Physiol. 2006 Jun;290(6):G1105-13.
34. Woodford K. A2 Milk, Farmer Decisions, and Risk Management. In: O'Reilly S, Keane M, Enright.P., editors. Proceedings of the 16th International Farm Management Association Congress, Peer Reviewed Papers Cork University College; July 2007. p. 641-8.