Intended for Health Care Professionals
• BIOLOGY AND POTENTIAL EFFECTS OF A1 BETA-CASEIN-DERIVED BETA-CASOMORPHIN-7

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BIOLOGY AND POTENTIAL EFFECTS OF A1 BETA-CASEIN-DERIVED BETA-CASOMORPHIN-7

Executive summary

Cow’s milk and dairy products are a major food source. A major protein component of cow’s milk is β-casein, of which there are two primary variants, A1 and A2. Digestion of A1 β-casein, but not A2 β-casein, yields the peptide β-casomorphin-7, an exorphin, which can influence opioid signalling pathways.

Key points

• Digestion of A1 β-casein, but not that of A2 β-casein yields β-casomorphin-7 (BCM-7), an exogenous opioid peptide (exorphin) that can potently activate opioid receptors throughout the body
• Opioid receptors are important regulators of signalling processes throughout the body, including the gastrointestinal tract, immune system, and the central nervous system
• Excessive exposure to A1 β-casein is linked to several clinical disorders, including abnormal gastrointestinal function, atherosclerosis/ischaemic heart disease, type 1 diabetes, and augmentation of the behavioural symptoms of schizophrenia and autism
• BCM-7 is primarily metabolised by dipeptidyl peptidase 4 (DPP4). Individuals with low DPP4 activity, particularly infants, are unable to breakdown BCM-7 and experience more severe symptoms
• Reducing or eliminating the consumption of A1 β-casein, and replacing it with another major protein source, such as A2 β-casein, may avoid some of these disorders or improve their symptoms
**Introduction**

β-casein is a major protein expressed in human and cow’s milk and is present in many food products derived from milk. In cow’s milk, two primary variants of β-casein, termed A1 and A2, and several rarer sub-variants have been identified. A1 and A2 β-casein differ in their protein structure by a substitution of the amino acid at position 67. A1 β-casein contains a histidine residue at this position, which allows cleavage of the preceding seven amino acid residues to yield the peptide β-casomorphin-7 (BCM-7) (Figure 1A). A2 β-casein contains a proline residue, which prevents cleavage of this peptide. The sub-variant B β-casein also has a histidine at position 67, and its cleavage also results in the generation of BCM-7, but this variant is much less frequent than A1 or A2 β-casein in the milk of cows of European origin. Nine other variants have been identified to date in the *Bos* genus (A3, C, D, E, F, G, H1, H2 and I, of which a histidine occurs at position 67 in variants C, F and G) based on studies of various breeds of cattle or conducted in different geographical locations, although these variants are much less common than the A1 and A2 variants.

The other major peptides formed by the cleavage of β-casein are indicated in Figure 1B. The digestion of β-casein is rapid, and is thought to be completed within about 60 min under gastro-analogous conditions. BCM-7 has the potential to cross the gastrointestinal wall to enter the systemic circulation, where it may influence systemic and cellular activities by acting on opioid receptors. BCM-7 may also be able to cross the blood–brain barrier to influence central nervous system activities. β-casein proteins derived from human breast milk, goat’s milk, and sheep’s milk are homologous to bovine A2 β-casein, based on the published protein sequences.
Figure 1. (A) Cleavage of A1 β-casein at position 67 yields the peptide β-casomorphin-7. (B) Other sites within β-casein targeted by gastrointestinal enzymes that yield peptide molecules. (B) Reprinted from Jinsmaa and Yohiskawa (1999).
BCM-7 is an exorphin that influences opioid signalling throughout the body

BCM-7 and other derivatives of β-casein are potent exogenous agonists of opioid receptors (exorphins), with greatest affinity for μ opioid receptors. The role of opioid receptors in mediating the effects of BCM-7 is supported by the finding that naloxone, a μ opioid receptor-specific competitive antagonist, prevents many of the effects of BCM-7, including effects on gastrointestinal motility and mucus secretion, lymphocyte proliferation, and histamine release from peripheral leukocytes. The affinity of bovine BCM-7 to opioid receptors is approximately 10 times greater than that of human BCM-7, as it requires a 10-fold greater naloxone concentration to prevent receptor binding.

Opioid receptors are expressed by many cell types in most organs. Levels of μ opioid receptors are highest in the hypothalamus, cerebral cortex, and spleen, moderate in the cerebellum, intestine, kidney, adrenal, and reproductive organs, and lowest in the lung and liver. μ opioid receptors are not expressed in the stomach, heart, or endothelium. Opioid receptors are also expressed on inflammatory cells, including lymphocytes and leukocytes.

Experimental studies have shown that BCM peptides and analogues may be able to cross the blood–brain barrier. This was particularly evident in regions with ‘leaky’ capillaries, such as the pineal gland, the neurohypophysis, and the choroid plexus. An autopsy study revealed BCM immunoreactivity in several brain regions, including the brain stem, while a clinical study detected BCM-8 in the cerebrospinal fluid of pregnant and lactating women. Therefore, BCM peptides may influence central signalling pathways after crossing the blood–brain barrier.

BCM-7 is metabolised by dipeptidyl peptidase 4 (DPP4)

BCM-7, and other related peptides with an amino acid sequence of Tyr-Pro-Phe-Pro-Gly-Pro-Ile, including their C-terminally shortened fragments, are primarily degraded by DPP4. DPP4 is a protease that selectively removes the N-terminal dipeptide from peptides bearing a Pro or Ala residue at position 2. It is principally expressed on T lymphocytes and a soluble form exists in plasma. A recent study of infants revealed that infants with apparent life-threatening apnoea had markedly elevated BCM-7 levels but much lower serum DPP4 activity compared with healthy infants of the same age. Those results suggested that individuals with lower DPP4 activity may be more prone to the potential adverse effects of BCM-7; however, the results need to be confirmed in further studies.
Clinically relevant effects of A1 β-casein and BCM-7

As shown in Figure 2, as BCM-7 has the potential to cross the gastrointestinal wall and blood–brain barrier, it may be able to influence activities in most systems throughout the body, partly because of the highly ubiquitous expression of opioid receptors.

Figure 2. A1 β-casein and BCM-7: Production, absorption, and potential targets.

 Studies have shown direct effects of BCM-7 on several gastrointestinal functions. For example, BCM-7 has been reported to reduce the frequency and amplitude of intestinal contractions, thus slowing gastrointestinal motility,9,10,26-28 and to stimulate mucus release.11,29,30 BCM-7 also inhibits lamina propria lymphocyte proliferation,12 which may affect susceptibility to infection.

BCM-7 also has immunomodulatory effects, including triggering of histamine release from peripheral leukocytes,13 secretagogue effects on peritoneal mast cells,31 and suppression of lymphocyte proliferation.12 Similarly, A1 β-casein has marked pro-
atherogenic effects, promoting low-density lipoprotein (LDL) oxidation and the generation of autoantibodies to oxidized LDL, both of which might contribute to the progression of atherosclerosis.

A1 β-casein and BCM-7 are also implicated in the pathogenesis of type 1 diabetes via two mechanisms. In the first, consumption of A1 β-casein induces the production of autoantibodies that ultimately cause autoimmune-mediated killing of pancreatic β cells. Illustrating the second pathway, A1 β-casein induced diabetes in non-obese diabetogenic mice via opioid receptors, as the diabetogenic effects of A1 β-casein were prevented by the μ-receptor-specific antagonist naloxone.

These immunomodulatory and pro-atherogenic effects of A1 β-casein may be responsible for the increased risk of increased risk of heart disease (Figure 2A) and type 1 diabetes (Figure 2B) in populations associated with high per capita A1 β-casein consumption.

The consumption of β-casein has also been linked with the worsening of symptoms of schizophrenia and autism. These effects were attributed to the opioid activities of BCM-7 and to oxidative stress, causing neurological deficits that manifested as symptoms of schizophrenia and autism.
Figure 3. Correlations between A1 β-casein supply per capita in 1990 and ischaemic heart disease (A) and type 1 diabetes (B). (A) Correlation between A1 β-casein supply per capita in 1990 and ischaemic heart disease in 1995 in 20 countries. $r = 0.76$ (95% confidence interval: 0.48–0.90; $p \leq 0.0001$). (B) Correlation between A1 β-casein supply per capita in 1990 and incidence of type 1 diabetes (1990–1994) in children aged 0–14 years in 19 countries. $r = 0.92$ (95% confidence interval: 0.72–0.97; $p < 0.0001$). Dotted lines are the 95% confidence limits of the regression line. Reprinted from Laugesen and Elliott (2003).

Rationale for avoiding consumption of products containing A1 β-casein

Experimental and small-scale clinical studies, as well as cases in the lay media, have provided evidence supporting the benefits of removing A1 β-casein from the diet. For example, switching to a gluten- and casein-free diet ameliorates some of the symptoms of autism.\textsuperscript{51-54} Similarly, some food disorders, such as lactose intolerance, may be wrongly diagnosed and could resolved by replacing A1 β-casein with A2 β-casein.\textsuperscript{55, 56} Avoidance of A1 β-casein may also prevent the excess immunomodulatory activity associated with type 1 diabetes, neurological disorders, and ischaemic heart disease. More studies, including randomized controlled trials, observational cohort studies and case reports, are needed to confirm the potential clinical benefits of reducing A1 β-casein consumption.

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More in this series

- Beta-casein and digestive, respiratory and immune functions
- Beta-casein variants and neurological conditions
- Beta-casein and infant growth and development

Disclosure

This evidence-based report and others in the same series were developed by the medical communications branch of Edanz Group Ltd (Hong Kong) to summarize key research findings associated with bovine A1/A2 β-casein consumption. The reports were commissioned by A2 Corporation Ltd (Auckland, New Zealand).
BETA-CASEIN AND DIGESTIVE, RESPIRATORY, AND IMMUNE FUNCTIONS
BETA-CASEIN AND DIGESTIVE, RESPIRATORY, AND IMMUNE FUNCTIONS

Executive summary

Cow's milk and dairy products are a major food source. A major protein component of cow's milk is β-casein, of which there are two primary variants, A1 and A2. Digestion of A1 β-casein yields the peptide β-casomorphin-7, an exorphin. β-casomorphin-7 can target opioid receptors in various systems to influence digestion, respiration, and immunity. Consumption of A2 β-casein instead of A1 β-casein could have beneficial effects on these systems by avoiding the unwanted effects of the latter.

Research highlights

• Digestion of A1 β-casein, but not that of A2 β-casein yields β-casomorphin-7 (BCM-7), an exogenous opioid peptide (exorphin) that can potently activate opioid receptors throughout the body
• Opioid receptors are important regulators of gastrointestinal function, including motility, mucus secretion and hormone/incretin secretion
  • Casein and its derivatives, including BCM-7, slow gastrointestinal motility, which may cause constipation
  • BCM-7 significantly increases intestinal mucus secretion via opioid signalling pathways, which may influence commensal bacteria and drug absorption
  • Reducing A1 β-casein consumption could alleviate gastrointestinal disturbances
• Many immune cells express the µ-opioid receptor, which has immunosuppressive activity 
in vitro and in vivo
  • BCM-7 disturbs immune cell function in vitro
  • Consumption of products containing A2 β-casein, which does not yield BCM-7, instead of those containing A1 β-casein, could avoid disruption to immune cell function leading to symptoms of food intolerance
• Opioid receptors play an important role in controlling respiration
  • Activation of opioid receptors in the brainstem, particularly the pons, can suppress respiration
  • BCM-7 and other opiates may be involved in apparent life-threatening events in infants


Introduction

β-casein is a major protein expressed in human and cow’s milk and is present in many food products derived from milk. In cow’s milk, two primary variants of β-casein, termed A1 and A2, and several much rarer sub-variants have been identified. A1 and A2 β-casein differ in their protein structure by a substitution of the amino acid at position 67. A1 β-casein contains a histidine residue at this position, which allows cleavage of the preceding seven amino acid residues, generating the peptide β-casomorphin-7 (BCM-7). A2 β-casein contains a proline residue at this position, which prevents cleavage of this peptide.\(^1\) The sub-variant B β-casein also has a histidine at position 67, and its cleavage also results in the generation of BCM-7, but this variant is much less frequent than A1 or A2 β-casein in the milk of cows of European origin.

BCM-7 can cross the gastrointestinal wall to enter the systemic circulation and influence systemic and cellular activities via opioid receptors. Moreover, BCM-7 and other derivatives of β-casein are potent exogenous agonists—exorphins—for opioid receptors, with the greatest affinity for µ-opioid receptors.\(^2\)

Opioid receptors are expressed in many organs, notably the gastrointestinal tract,\(^3, 4\) immune cells,\(^5, 6\) and the central nervous system, particularly in the regions controlling respiration.\(^7\) Activation of these receptors can have unwanted or unexpected effects on gastrointestinal, immune, and respiratory functions. Therefore, it is important to evaluate the potential effects of BCM-7 and related milk-derived peptides on the functions of these systems.

Effects of BCM-7 on intestinal motility

Opioid receptors play a physiologically important role in controlling gastrointestinal function, including regulating gastrointestinal motility, mucus production and hormone/incretin production. Several studies have provided direct evidence that casein and its derivatives, particularly BCM and related peptides, decrease gastrointestinal motility (Figure 1), in part by reducing the frequency and amplitude of intestinal contractions.\(^8-12\) By contrast, soy protein, which cannot be cleaved to form BCMs, does not exert these effects.\(^9\) BCM-7 in particular can mimic the effects of opioids, in some cases leading to constipation. The role of opioid receptors in mediating these effects was confirmed, as co-treatment with an opioid receptor antagonist suppressed the effects of casein.\(^9\)
Effects of BCM-7 on the gut’s immune system: mucus secretion and lymphocyte activity

Gastrointestinal mucus secretion is at least partly regulated by opioid receptors; it is suppressed by opioid antagonists, such as naloxone, and increased by morphine. Gastrointestinal mucus serves as a protective barrier between the epithelium and the lumen, containing potentially harmful compounds and microorganisms, as well as a lubricant to help food passage.
Studies have shown that dietary peptides, including BCM-7, stimulate mucus release via μ-opioid receptors (Figure 2). Although the clinical relevance of this effect is not fully understood, excessive mucus secretion may interfere with commensal bacteria or alter gastrointestinal uptake of nutrients or drugs.

Another component of the gut's immune system is the lamina propria lymphocytes. These cells play an important role in innate immunity and protection against pathogens in the intestinal lumen. However, abnormal activity of the gut's immune system is implicated in the aetiology of gastrointestinal disorders, such as inflammatory bowel disease and food allergies. At least two studies have shown that BCM-7 alters lymphocyte proliferation in vitro through a pathway mediated by opiate receptors. The first of these studies showed suppressive effects of BCM-7 on lymphocyte proliferation at all concentrations tested, while the second study showed suppressive effects of low BCM-7 doses and stimulatory effects at higher doses. Considering that both studies were performed in vitro, more studies are needed to confirm the physiological relevance of these immunomodulatory effects of BCM-7 in animals and humans.

Figure 2. BCM-7 significantly enhances mucus secretion in isolated rat jejunum. Reprinted from Trompette et al (2003).

A1 protein avoidance could lessen gastrointestinal disturbances

The reports described above suggest that the consumption of products containing solely A2 β-casein and exclusion of those containing A1 β-casein could have some health benefits by maintaining the nutritional benefits associated with milk consumption while excluding the negative effects of A1 β-casein-derived BCM7 on gastrointestinal function. One gastrointestinal disorder commonly associated with milk consumption is lactose intolerance. However, some patients may have food allergy rather than intolerance, or they may
adversely react to other components of milk. In this way, reducing or stopping the intake of A1 protein could provide a first step toward isolating the cause of the gastrointestinal disturbance. Indeed, recent media reports have highlighted this possibility in a child with apparent lactose intolerance who did not experience gastrointestinal symptoms after switching to products containing A2 protein, suggesting that this child experienced an immune response to a component of A1 protein.

Prospective, randomized controlled studies are needed to confirm the validity of such an approach, but clinicians should be aware of the effects of BCM-7 on gastrointestinal motility, mucus secretion and immune function, and could support such a strategy in clinical practice.

**Immunomodulatory effects of exorphins**

While the immunomodulatory effects of morphine are generally well established, the potential immunomodulatory effects of β-casein and its cleaved peptides were first identified in the 1980s. Since then, it has become apparent that exorphins, including BCM-7, have immunomodulatory properties. For example, BCM-7 was reported to trigger histamine release from peripheral leukocytes and to have secretagogue effects on peritoneal mast cells. Studies have shown that BCM-7 alters lymphocyte proliferation in vitro through a pathway mediated by opiate receptors. The first of these studies showed suppressive effects of BCM-7 on lymphocyte proliferation at all concentrations tested (Figure 3), while the second study showed suppressive effects of low BCM-7 doses and stimulatory effects at higher doses.

Clinically, BCM-7 may also stimulate excessive histamine release, resulting in activation of immune responses. Impaired immune function may also increase susceptibility to infection and other potentially severe diseases, as has been reported for morphine. Additional studies are needed to establish the specific immunomodulatory effects of BCM-7 and related peptides, and to determine their clinical implications.
A1-derived BCM-7 and respiratory function

Opioid receptors, including µ-opioid receptors, are widely expressed in the central nervous system, including in sites associated with respiration control in the pons. Consequently, activation of these receptors by morphine and other opioids can induce respiratory depression, which can be reversed by antagonists, such as naloxone.

Peptides derived from casein, including BCM-7, have been implicated in the aetiology of sudden infant death syndrome. For example, Wasilewska et al. noted that infants with apparent life-threatening events had higher serum levels of BCM-7 after apnoea compared with healthy infants of the same age. One explanation for their findings was that the level of dipeptidyl peptidase 4 activity, which degrades short peptides in blood, was reduced in these infants, resulting in abnormally high levels of BCM-7. Similar findings were reported for other BCMs and β-endorphins. Hedner and Hedner noted that BCMs can readily cross the blood–brain barrier in newborn rabbits and cause dose-related depressions of respiratory frequency and tidal volume. They found that BCM-7 was equipotent to morphine, and its effects were reversed or prevented by naloxone, a µ-opioid receptor antagonist.

Further clinical and experimental studies are needed to evaluate the clinical relevance of BCM-7 in respiratory function and dysfunction in infants and in adults. Studies should also seek to confirm the association between BCM-7 and apparent life-threatening events in infants, and whether avoidance of some protein sources could reduce the incidence of such events.
References


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• BETA-CASEIN VARIANTS AND NEUROLOGICAL CONDITIONS
• BETA-CASEIN PROTEINS AND INFANT GROWTH AND DEVELOPMENT

Disclosure

This evidence-based report and others in the same series were developed by the medical communications branch of Edanz Group Ltd (Hong Kong) to summarize key research findings associated with bovine A1/A2 β-casein consumption. The reports were commissioned by A2 Corporation Ltd (Auckland, New Zealand).
BETA-CASEIN VARIANTS AND NEUROLOGICAL CONDITIONS
BETA-CASEIN VARIANTS AND NEUROLOGICAL CONDITIONS

Executive summary

Consumption of cow’s milk protein, or more specifically the casein fraction, has been implicated in modulating behaviour and aggravating symptoms associated with neurological conditions.1–3

Around 30% of cow’s milk protein is β-casein, of which there are two primary variants, A1 and A2. Digestion of A1 β-casein (A1) yields the peptide β-casomorphin-7 (BCM-7), a widely characterised exorphin, with the potential to be absorbed into the circulation and cross the blood–brain barrier; A2 β-casein is not reported to yield BCM-7.

It is hypothesised that BCM-7 augments the behavioural symptoms of several neurological diseases, including autism and schizophrenia, possibly via excessive activation of opioid signalling pathways in the brain that have been characterised in vitro.

Research highlights

• Digestion of A1 β-casein, but not that of A2 β-casein yields β-casomorphin-7 (BCM-7), an exogenous opioid peptide (exorphin) that can potently activate opioid receptors in the central nervous system

• The serum/urine levels of casein, BCM-7, and antibodies to casein were reported to be elevated in some people with neurological diseases, including autism and schizophrenia

• A1 consumption, via BCM-7, may activate opioid signalling pathways in the central nervous system to augment the behavioural symptoms of conditions including autism and schizophrenia

• In infants, consumption of cow’s milk formula and elevated blood BCM-7 levels were associated with delayed psychomotor development and abnormally high muscle tone

• A1-derived BCM-7 may induce oxidative stress by disrupting glutathione uptake or oxidizing lipoproteins

• Oxidative stress reduces methylation capacity and induces neurological deficits that are associated with the symptoms of autism and schizophrenia

• Consumption of a diet excluding A1 β-casein could help to avoid augmentation of the behavioural symptoms of autism and schizophrenia, and prevent delays in psychomotor development

Introduction
β-casein is a major protein expressed in human and cow’s milk and is present in many food products derived from milk. In cow’s milk, two primary variants of β-casein, termed A1 and A2, and several rarer sub-variants have been identified. A1 and A2 β-casein differ in their protein structure by a substitution of the amino acid at position 67. A1 β-casein contains a histidine residue at this position, which allows cleavage of the preceding seven amino acid residues to yield the peptide β-casomorphin-7 (BCM-7). A2 β-casein contains a proline residue at this position, which prevents cleavage of this peptide. The sub-variant B β-casein also has a histidine at position 67, and its cleavage also results in the generation of BCM-7, but this variant is much less frequent than A1 or A2 β-casein in the milk of cows of European origin.

BCM-7 has the potential to cross the gastrointestinal wall and the blood–brain barrier, so it may influence peripheral and central systems. In fact, BCM-7 has been linked with several neurological disorders, including autism, schizophrenia, respiratory depression/apnoea, and psychomotor development.

**Associations of β-casein with autism and schizophrenia**

Autism spectrum disorders are principally associated with impaired social functioning and communication, and limited flexibility of thought and behaviour. Several studies have reported a link between casein and autism spectrum disorders, including elevated urinary peptide secretion and the presence of antibodies to casein in individuals with autism. However, some studies have reported no such association. Associations between casein, particularly antibodies to casein, and schizophrenia have also been reported.

**Central effects of BCM-7 in autism and schizophrenia**

These effects of casein augmenting the symptoms of autism and schizophrenia are most likely attributable to exorphin activity in the brain. Indeed, it was reported that BCM-7, a product of A1 β-casein digestion, significantly reduced normal behaviours, such as rearing, walking and grooming in rats, and enhanced abnormal activities, such as explosive motor behaviour, circling and decreased social interaction (Figure 1). These behavioural effects of BCM-7 were caused by its interaction with opioid receptors, as the effects were abolished by the specific opiate-receptor antagonist naloxone. BCM-7 also induced fos-like immunoreactivity in brain regions relevant to schizophrenia, particularly the prefrontal cortex, the nucleus accumbens, the bed nucleus of the stria terminalis, and the caudate–putamen.
Figure 1. Behavioural effects of BCM-7 in rats. Drawn based on data presented in Sun and Cade (1999).\textsuperscript{17} A, explosive motor behaviour; B, autonomic changes (pupil dilation, rapid respiration); C, circling; D, reduced sound response; E, decreased social interaction; E, abnormal feelings (biting or lipping feet or tail); F, hyperemotionality; G, catalepsy.

BCM-7 may also augment the symptoms of schizophrenia and autism by inducing oxidative stress in the brain. \textit{In vitro}, BCM-7 was reported to lower cellular levels of glutathione, an antioxidant, by inhibiting cysteine uptake.\textsuperscript{19} \(\beta\)-casein can also promote low-density lipoprotein (LDL) oxidation,\textsuperscript{20} which is normally associated with atherosclerosis. However, abnormal lipid oxidation may also occur in the central nervous system, and may exacerbate the oxidative environment in neurological disorders like schizophrenia.\textsuperscript{21} This oxidative environment can result in impaired methylation of DNA and phospholipids, for example, and neurological deficits that ultimately manifest as symptoms of schizophrenia and autism (Figure 2).\textsuperscript{22}
BCM-7 and psychomotor development

BCM-7 may also affect other neurological activities, including psychomotor development. Kost et al.\textsuperscript{9} reported that immunoreactivity of human and bovine BCM-7 could be detected in breast-fed and formula-fed infants, respectively, within the first 3 months of life. Notably, elevated bovine BCM-7 immunoreactivity was associated with delayed psychomotor development and abnormally high muscle tone. By contrast, the opposite was found for human BCM-7, as infants with the highest human BCM-7 immunoreactivity showed the best psychomotor development. Further studies are needed to confirm these findings, and to evaluate the impact of diets aimed at avoiding A1 $\beta$-casein.

Opportunities for managing autism, schizophrenia, and psychomotor development

Several small-scale studies have demonstrated that switching to a gluten- and casein-free diet may ameliorate some of the symptoms of autism\textsuperscript{23-26} Considering the potential effects of BCM-7, switching patients to a diet excluding A1 $\beta$-casein could help uncover causative factors
in autism spectrum disorders and schizophrenia. Current studies have focused on the removal of gluten and casein from the diet; well-designed, prospective studies are needed to confirm the specific clinical effects of A1 β-casein, and the benefits of replacing A1 β-casein with A2 β-casein to avoid augmenting the symptoms of autism and schizophrenia. Provision of breast milk or cow’s milk formula lacking A1 β-casein may also help to prevent delays in psychomotor development.

References


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• Beta-casein and infant growth and development

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BETA-CASEIN PROTEINS AND INFANT GROWTH AND DEVELOPMENT
Executive summary

While breast milk is recommended for infants, breast feeding may not be possible for medical or personal reasons, in which case milk formula is used instead. Milk formula is usually based on cow’s milk with the addition of essential nutrients and vitamins. A major protein component of cow’s milk is β-casein comprising ~30% of total milk protein, of which there are two primary variants, A1 and A2. Owing to subtle structural differences between these proteins, digestion of A1, but not A2, yields the peptide β-casomorphin-7 (BCM-7), an exorphin that may interact with a variety of body systems. A range of studies have linked A1 or BCM-7 to an increased risk of type 1 diabetes in some infants, immune responses, digestive disorders, and respiratory dysfunction. The A2 protein, which reportedly does not produce BCM-7, is more comparable to the human β-casein protein, which accounts for >80% of the protein in mothers’ breast milk. Therefore, a formula based on the A2 protein, excluding A1 protein, may more closely mimic breast milk and may help to maintain optimal growth and development.

Research highlights

• Breast milk is preferred, but may not be available for all infants, meaning a cow’s milk-based formula may be required
• A major protein component of cow’s milk is β-casein, making up ~30% of total milk protein. There are two major variants of β-casein, A1 and A2
• Owing to a subtle structural difference, digestion of A1, but not A2, yields β-casomorphin-7 (BCM-7), an exogenous opioid peptide (exorphin) that can potentially interact with a variety of body systems
• A2 is structurally more comparable than A1 to the β-casein protein in human breast milk, which accounts for >80% of the total protein content
• The immature digestive system of infants compared with that of adults increases the likelihood of incomplete cleavage of A1 β-casein. This leads to production of BCM-7 and its potential absorption into the blood stream and across the blood–brain barrier
• Following its production in the digestive tract, BCM-7 can potentially impart adverse effects on the digestive system or on other organs upon absorption into the systemic circulation
• A growing body of research has shown associations of A1 or BCM-7 with a range of adverse effects, including increased risk of type 1 diabetes in some children, intolerance reactions, and digestive disorders
• More recent studies have reported correlations between the levels of BCM-7 derived from A1-containing formulas in infants and both delays in psychomotor development and respiratory dysfunction
• Consumption of an infant formula containing only A2 β-casein, with the exclusion of A1, may therefore help to maintain a range of functions in growing and developing infants

Introduction

Breast milk is the preferred source of nutrition for infants. The World Health Organization recommend that infants should be exclusively breastfed for the first 6 months of life, and that breastfeeding should be continued for up to 2 years or beyond together with appropriate solid foods. However, not all infants can be breastfed, and some families may not have access to a healthy wet-nurse or human milk-bank. In such situations, the family will need to use commercial or home-prepared infant formula instead. Most infant formulas are produced from cow’s milk, as it is a relatively cheap source of protein and nutrients, and is abundantly available. However, the protein compositions of breast milk and cow’s milk differ substantially. For example, breast milk is whey dominant, with an approximate casein to whey ratio of 40:60, ranging from 10:90 in early lactation to 50:50 in late lactation. By contrast, cow’s milk and infant formula have casein to whey ratios as high as 80:20.

β-casein is a major protein expressed in human and cow’s milk and is present in many food products derived from milk. In cow’s milk, two primary variants of β-casein, termed A1 and A2, and several much rarer sub-variants have been identified. A1 and A2 β-casein differ in their protein structure by a substitution of the amino acid at position 67 (Figure 1A). β-casein, like other proteins, is an important source of amino acids and facilitates mineral transport, but can be broken down into smaller bioactive peptides. A1 β-casein contains a histidine residue at this position, which allows cleavage of the preceding seven amino acid residues, generating the peptide β-casomorphin-7 (BCM-7). A2 β-casein contains a proline residue at this position, which prevents cleavage of this peptide. The protein structure of β-casein in breast milk is similar to that of A2 β-casein in cow’s milk (Figure 1B); therefore, human β-casein is not susceptible to this mode of cleavage.
BCM-7 has a demonstrated potential to cross the gastrointestinal wall to enter the systemic circulation and influence systemic and cellular activities via opioid receptors. Moreover, BCM-7 and other derivatives of β-casein are potent exogenous agonists—exorphins—for opioid receptors, with the greatest affinity for μ receptors. Consequently, BCM-7 has the potential to influence the activities of a variety of organs/systems, notably the digestive system and immune cells. It may also be involved in various disorders in infants, including type 1 diabetes and respiratory dysfunction, and may influence central nervous system activity.

**Figure 1.** (A) Cleavage of A1 β-casein at position 67 yields the peptide β-casomorphin-7. (B) Sequence comparison of A1 and A2 β-casein in cow’s milk and the corresponding sequence in human β-casein.

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BCM-7 is reported as:
- A strong exogenous opioid
- A catalyst for oxLDL formation

A1-derived BCM-7 and the digestive system

Andiran et al. reported that chronic constipation and the development of anal fistulas were significantly associated with the volume of cow’s milk consumed and a shorter duration of breastfeeding in infants.\(^8\) This phenomenon may be related to the morphine-like effects of BCM-7.\(^9,10\)

The digestive tract of infants is very immature, particularly in terms of enzyme expression profiles and commensal bacteria,\(^11\) undergoing continual development from birth to weaning.\(^12\) Because proteins are principally digested in the intestinal tract in infants, rather than in the stomach as in adults, the likelihood of incomplete digestion of \(\beta\)-casein to amino acids is much greater in infants. Furthermore, the neonatal gut is designed to absorb relatively large macromolecules, particularly lactoglobulins, from breast milk. A consequence of these essential features of the infant gut may include increased generation and uptake of BCM-7, which may directly affect the functions of the digestive tract by slowing gastrointestinal transit, altering mucus secretion, and may facilitate the development of anal fistulas. The protein fragments may also have important roles in immunologic and allergic reactions.\(^13\)

A1-derived BCM-7 and immune function

While the immunomodulatory effects of morphine are generally well established, the potential immunomodulatory effects of \(\beta\)-casein and its cleaved peptides were first identified in the 1980s.\(^14,15\) Since then, it has become apparent that exorphins, including BCM-7, have immunomodulatory properties. For example, BCM-7 was reported to trigger histamine release from peripheral leukocytes\(^16\) and to have secretagogue effects on peritoneal mast cells.\(^17\) Studies have shown that BCM-7 alters lymphocyte proliferation in vitro through a pathway mediated by opiate receptors.\(^18,19\) The first of these studies showed suppressive effects of BCM-7 on lymphocyte proliferation at all concentrations tested,\(^18\) while the second study showed suppressive effects of low BCM-7 doses and stimulatory effects at higher doses.\(^19\)

Clinically, BCM-7 may induce allergic reactions by stimulating excessive histamine release, which may lead to localised pseudoallergic skin reactions or airway inflammation.\(^16,20\) Impaired immune function may also increase susceptibility to infection and other potentially severe diseases, as has been reported for morphine.\(^21\) Although additional studies are needed to establish the specific immunomodulatory effects of BCM-7 and related peptides, and to determine their clinical implications, these adverse events could be avoided by excluding A1 \(\beta\)-casein from the diet.
A1 β-casein and type 1 diabetes

Type 1 diabetes is characterised by autoimmune-mediated destruction of pancreatic β cells. Its incidence is progressively increasing in many countries. One explanation for this is that environmental factors play major roles in its pathogenesis.

A link between cow’s milk and type 1 diabetes in animals was first reported in 1984; a link to type 1 diabetes in humans was first reported in 1990. A subsequent study proposed that early exposure to cow’s milk may increase the risk of type 1 diabetes by approximately 1.5 times. Since then, several published studies have supported this association, although other studies have found no association between antibodies to cow’s milk and the risk of type 1 diabetes.

The identification of A1 and A2 β-casein, and the increased understanding of their differing effects on immune function, prompted the hypothesis that the discrepancies in epidemiological findings may be, at least partly, attributable to the main type of β-casein consumed in each country. In 1999, in an analysis of children aged 0–14 across 10 countries/regions, Elliott et al. reported that, while total cow’s milk protein consumption was not significantly correlated with the incidence of type 1 diabetes ($r = 0.402$), the consumption of A1 β-casein was ($r = 0.726$). These findings were confirmed by two other independent studies involving a larger number of countries/regions (Figure 2). A study published in 2006 provided further support for the diabetogenic effects of A1 β-casein.
Figure 2. Correlation between A1 β-casein supply per capita in 1990 and incidence of type 1 diabetes (1990–1994) in children aged 0–14 years in 19 countries. $r = 0.92$ (95% confidence interval: 0.72–0.97; $p < 0.0001$). Dotted lines are the 95% confidence limits of the regression line. Reprinted from Laugesen and Elliott (2003).35

To better understand the relationship between A1 β-casein and risk of diabetes, Birgisdottir et al. compared the risk of type 1 diabetes among children and adolescents in Iceland and Scandinavia.37 They found a significant correlation between the calculated consumption of A1 β-casein among 2-year-old children with the incidence of type 1 diabetes at the age of 0–14 years ($r = 0.9$, $P = 0.037$). On the other hand, A1 β-casein consumption among 11–14-year-old individuals was not associated with the incidence of type 1 diabetes. Their data also suggested that the lower consumption of A1 β-casein from cow’s milk was a contributor to the lower incidence of type 1 diabetes in Iceland than in Scandinavia. Therefore, avoiding the consumption of A1 β-casein may reduce the risk of developing type 1 diabetes in adolescence.

A1-derived BCM-7 and respiratory function

Peptides derived from casein, including BCM-7, have been implicated in the aetiology of sudden infant death syndrome.6 For example, Wasilewska et al. noted that infants with apparent life-
threatening events had higher serum levels of BCM-7 after apnoea compared with healthy infants of the same age. Similar findings were reported for other BCMs and β-endorphins. Hedner and Hedner noted that BCMs can readily cross the blood–brain barrier in newborn rabbits and cause dose-related depressions of respiratory frequency and tidal volume. They found that BCM-7 was equipotent to morphine, and its effects were reversed or prevented by naloxone, a µ-receptor antagonist.

**A2 protein and avoidance of A1 may be a more natural alternative to A1 cow’s milk**

Based on the information accumulated to date, it would appear that consumption of dairy products containing predominantly A1 β-casein may be associated with some adverse clinical outcomes in some susceptible infants and young children, including digestive disorders, immune disorders, type 1 diabetes, and respiratory dysfunction. By contrast, infants who are mainly given breast milk, which contains β-casein that is more comparable in terms of structure and digestion patterns to A2 than to A1 β-casein in cow’s milk, are at a lower risk of developing these disorders. For infants requiring milk formula because of limited availability of breast milk, the data published to date indicate that milk formula (or dairy products in older children) lacking A1 β-casein may help to avoid a range of adverse effects or reactions.

**References**


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Disclosure

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