

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.⁴ 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,⁵ schizophrenia,^{1, 6} respiratory depression/apnoea,^{7, 8} and psychomotor development.⁹

Associations of β -casein with autism and schizophrenia

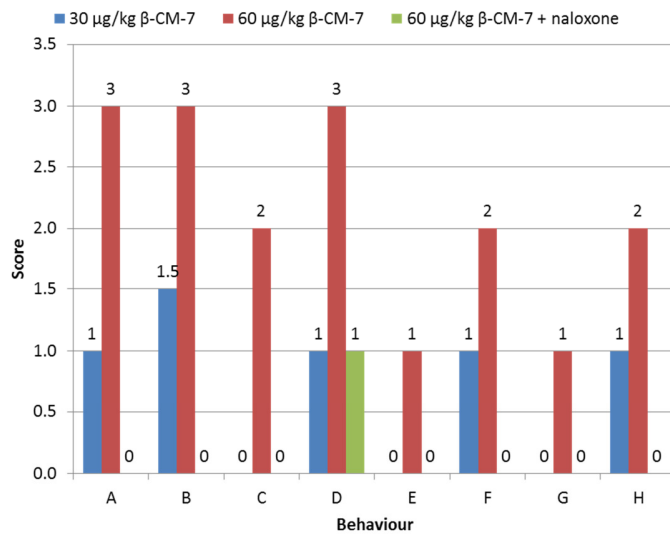
Autism spectrum disorders are principally associated with impaired social functioning and communication, and limited flexibility of thought and behaviour.¹⁰ Several studies have reported a link between casein and autism spectrum disorders, including elevated urinary peptide secretion and the presence of antibodies to casein in individuals with autism.^{1, 2, 5, 11} However, some studies have reported no such association.¹² Associations between casein, particularly antibodies to casein, and schizophrenia have also been reported.^{6, 13-16}

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.³ 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).¹⁷ 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

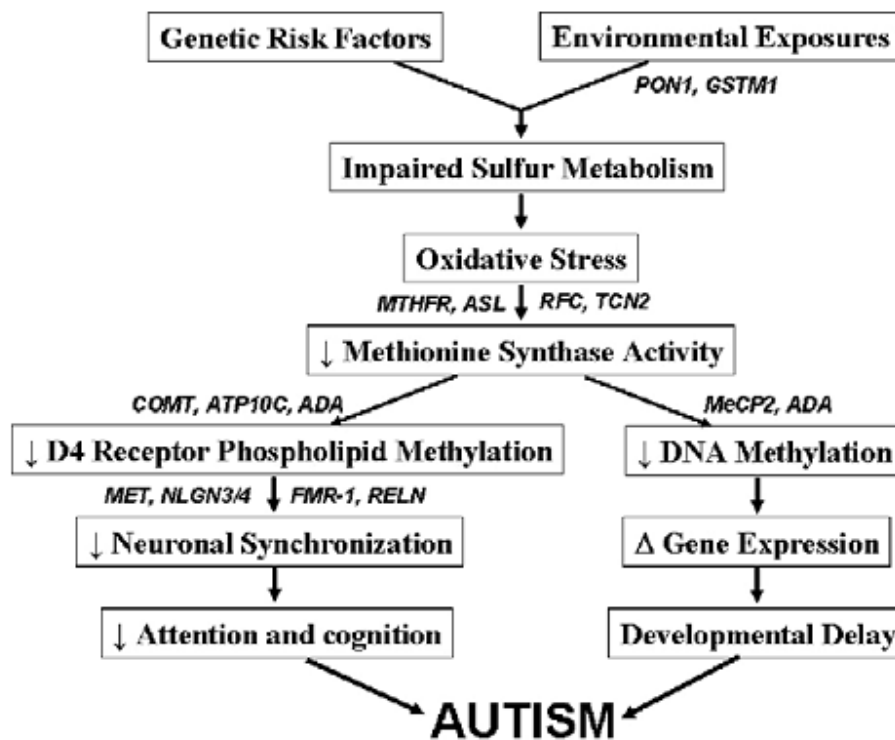
relevant to schizophrenia, particularly the prefrontal cortex, the nucleus accumbens, the bed nucleus of the stria terminalis, and the caudate–putamen.¹⁸

Figure 1. Behavioural effects of BCM-7 in rats. Drawn based on data presented in Sun and Cade (1999).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. *In vitro*, BCM-7 was reported to lower cellular levels of glutathione, an antioxidant, by inhibiting cysteine uptake.¹⁹ β-casein can also promote low-density lipoprotein (LDL) oxidation,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.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).²²

Figure 2. A redox/methylation hypothesis for autism. Reprinted from Deth et al. (2008).²²



BCM-7 and psychomotor development

BCM-7 may also affect other neurological activities, including psychomotor development. Kost et al.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 β -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,²³⁻²⁶ Considering the potential effects of BCM-

7, switching patients to a diet excluding A1 β -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.

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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).