A1/A2 Milk and β-Casomorphins: The Resurgence of Controversy

There is a growing global interest in the alternative milk product called A2 milk. A New Zealand–based company founded in 2000 advanced the hypothesis that genetic variants of β-casein may account for some milk-related health issues, such as digestibility and diabetes. For example, the hypothesis further suggests that traditional bovine milk that contains A1 β-casein may contribute to negative health effects, whereas A2 β-casein does not appear to exert these effects. The foundation of this hypothesis is that upon digestion, A1 β-casein releases β-casomorphin-7 (BCM-7), which triggers a cascade of events that increase inflammation and gastrointestinal discomfort. However, in a 2009 assessment of the BCM-7 clinical data on human health, the European Food Safety Authority found no relationship with purported negative outcomes (EFSA 2009).

Interestingly, a recent publication indicated variations in other positions, such as 18 (lysine for D variant) and 93 (leucine for variants H2 and I). Interestingly, there are considerable A2 β-casein homologies (>90%) in other mammalian milks, such as buffalo, sheep, and goat. As one would expect, there are also A1 β-casein high level homologies in the same species and lesser homologies among other mammals.

Several publications suggest bovine A1 β-casein, which contains histidine at position 67, is subject to proteolytic digestion that subsequently produces a seven amino acid residue, namely β-casomorphin-7. An in vitro study with bovine β-casein exposed to a variety of proteases, such as trypsin, chymotrypsin, or pancreatin, indicated several opioid peptides were obtained, including BCM-7, BCM-9, BCM-13, and BCM-21 (Jinsmaa and Yoshikawa 1999). These results were confirmed through a separate gastro-analogous digestion that simulated digestion processes among humans suggesting A2 β-casein may contribute to negative health effects, whereas A2 β-casein does not appear to exert these effects.

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The digestive product BCM-7 is not limited to A1 β-casein based on an ex vivo digestion system designed to mimic protein digestion processes among humans (Asledottir, Poulsen, Larsen, Le, Devold, and Vegarud 2018).

The most common forms among dairy cattle are A1 and A2 β-casein, which differ in amino acid histidine or proline, respectively, at position 67 of this protein structure. Other polymorphisms include A3, B, C, D, E, F, H1, H2, I, and G alleles (Kaminski, Cieslinska, and Kostyra 2007). Histidine is also at position 67 in B, C, F, and G variants. Both A1 and A2 forms have amino acid conditions over a 60 min period for a typical human adult (Schmelzer, Schops, Reynell, Ulbrich-Hofmann, Neubert, and Raith 2007). It is important to note that within infants who present an immature digestive tract, proteins are primarily digested in the gastrointestinal tract (Hamosh 1996). Therefore, it is likely that the digestion of β-caseins to their respective amino acids is incomplete.

Before examining the influence of β-casomorphins in bovine milk, it is important to explore the presence and function of these peptides in human milk (Jarmolowska, Sidor, Iwan et al. 2007), which are also found in casein hydrolysates—containing infant formula (Cattaneo, Stuknyte, Masotti, and De Noni 2017). Interestingly, the levels of different forms of BCM, such as BCM-7 and BCM-5, change throughout lactation. The highest concentrations of these BCM forms occur in colostrum and then gradually decrease with the period of lactation.

The human brain continues development from the third week of gestation through late adolescence, and probably throughout life (Stiles and Jermain 2010). During neurodevelopment, a series of complex, dynamic, and adaptive processes occur that contribute to structural and functional organization of the mature brain. These natural processes were lower in the presence of bovine BCM-7, which appeared to increase the formation and differentiation of astrocytes. These cells are the most abundant cell type within the central nervous system. In a model system of neurogenesis and applied to neural stem cells, this process was promoted by the presence of BCM-7 found in breast milk. Equally interesting, human milk BCM-7 contributed to the redox state and epigenetic modifications that appear to influence neural development (Trivedi, Zhang, Lopez-Toledano, Clarke, and Deth 2016).

A limited number of clinical studies among humans suggest A2 β-casein may be better tolerated and digested relative to A1 β-casein. In an 8-week crossover study among 41 subjects who self-reported intolerance to milk, the consumption of 750 mL of A1 milk over a two-week period described similar levels of intolerance, yet significant changes in stool consistency and bowel frequency compared with those consuming the same volume of A2 milk (Ho, Woodford, Kukuljan, and Pal 2014). There were not any significant differences in indicators of gut inflammation between the two groups.
In another study, 45 adult subjects who self-reported intolerance to milk participated in a double-blind, randomized, 2 x 2 crossover trial. They consumed 250 mL of either A1/A2 or A2 milk following each of two meals over a 14-day period. The intent of this study was to compare digestive symptoms and physiological markers of inflammation. The results suggested subjects consuming A1/A2 milk presented greater digestive symptoms associated with lactose intolerance, whereas the consumption of A2 milk did not aggravate these symptoms. Inflammatory markers, such as IL-4, IgG, IgE, and IgG1, were significantly lower in A2 milk consumers (Jianqin, Leiming, Lu, Yelland, Ni, and Clarke 2016). However, only 10 of the measured 60 comparisons were significant and favored consumption of A2 milk.

In a follow-up study, 600 adult subjects who reported lactose intolerance and digestive discomfort following milk consumption were assigned to consume 300 mL of conventional A1/A2 milk or A2 milk over a 7-day period. Results from this randomized, double-blind, crossover study indicated digestive symptoms were markedly reduced after consuming A2 milk versus conventional milk among lactose absorbers and lactose malabsorbers (He, Sun, Jian, and Yang 2017).

None of the three studies included a dietary control and all were of short duration, which did not allow for potential adaptation. Such adaptation was demonstrated in an earlier study on lactose intolerance (O’Connor, Eaton, and Savaiano 2015). Following a 21-day intervention among 32 adults consuming increasing (120 mL→240 mL) amounts of cow’s milk, their lactose intolerance was evaluated using the classic hydrogen breath test. At a three-month (26 subjects) and six-month (24 subjects) follow-up, the evidence indicated a reduced aversion to milk and an increased diet quality among lactose digesters and lactose mal digesters.

Some studies suggest a significant association between the intake of A1 milk and the incidence of type 1 diabetes (insulin-dependent diabetes mellitus, IDDM). For example, a 1999 published retrospective study (data from 1960 to 1991) among children (< 14 years old) from 10 countries indicated a strong correlation (r > 0.9; Spearman’s rank correlation) between casein A1 and B consumption and the incidence of IDDM (Elliott, Harris, Hill, Bibby, and Wasmuth 1999). There is a hypothesis that IDDM is strongly associated with an autoimmune phenomenon that reduces the number of pancreatic islet cells (Schranz and Lernmark 1998). This destruction may be exacerbated with the production of antibodies against beta-casein (Padberg, Schumm-Draeger, Petzoldt, Becker, and Federlin 1999). Data from nearly 1,300 sera samples obtained from 287 patients with IDDM, 386 siblings, 477 individual parents, and 107 health controls indicated all subjects presented antibodies against casein, with the highest anti-casein A1 titers among IDDM subjects and their siblings. These studies suggest an immune vulnerability to certain types of dietary proteins, such as β-casein, while a single study on BCM-7 suggests this peptide may suppress the immune defense system by inhibiting lymphocyte proliferation (Elitsur and Luk 1991).

These kinds of studies suggest BCMs are associated with a spectrum of immunological activities, such as chronic inflammatory responses, allergy, mucin production, lymphocyte proliferation, and skin reactions. When considering the dynamics of the immune system, one must reflect on the relationship between mucus secretion and innate immunity. A rodent model indicated that luminal exposure to BCM-7 may stimulate mucin secretion and thus contribute to gastrointestinal protection against enteric pathogens (Trompette, Claustre, Caillon, Jourdan, Chayvialle, and Plaisancie 2003). Similar results were observed in human HT-29-MTX cells (human colon adenoma cells that differentiated post-treatment into mature goblet cells using methotrexate), which in turn demonstrated increased MUC5A mRNA (> 200% after 24 hr) and enhanced secretion of mucin (169% of controls) upon exposure to BCM-7 (Zoghbi, Trompette, Claustre, et al. 2006).

Opioid peptides, such as BCM-7, have been associated with various physiological disorders; on the other hand, these peptides are potential modulators of numerous regulatory processes in the body. The inconsistencies in epidemiological data and variations in functional properties provide an interesting foundation for future research. The mechanisms of actions and the clinical significance of these peptides on the development and stability of various organ systems, such as digestive, developmental, and immune, among at-risk and general populations remain uncertain. Of course, the impact on the dairy industry and the subsequent composition and nutritional quality of milk products dominated by A2 β-casein pose additional investigative opportunities.

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